Retrieval induced forgetting in depression and schizophrenia: role of mood and the cholinergic system

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RETRIEVAL INDUCED FORGETTING IN DEPRESSION AND SCHIZOPHRENIA: ROLE OF MOOD AND THE CHOLINERGIC SYSTEM

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A thesis submitted in partial fulfilment of the requirements of the University of Westminster for the degree of Doctor of Philosophy

November 2012

Abstract

Retrieval-induced forgetting (RIF) is a robust phenomenon, which holds that recalling information from long-term memory can suppress the accessibility of related representations. Both inhibitory and interference processes have been identified as potential mechanisms that may underlie these automatic effects of retrieval. Depression and schizophrenia are known to be associated with inhibitory deficits and there is evidence demonstrating a reduced RIF among these disorders. Very few studies have however investigated RIF in these disorders and the mixed findings reported in the literature are inconclusive.

This programme of research addressed methodological issues surrounding the RIF procedure along with mediating factors contributing to the inhibitory processes that underlie this mechanism. These factors have been largely ignored thus far, however there is evidence that mediation of the cholinergic system with nicotine increases RIF whilst low mood reduces the RIF effect. In a series of studies, selected neuropsychological measures, RIF, smoking status and mood were assessed in a sample of individuals with clinical depression, individuals with schizophrenia, healthy control comparisons, a group of twin pairs diagnosed with schizophrenia and a group of healthy twin pairs.

Within depression and schizophrenia both groups demonstrated the standard pattern of RIF. However this effect was significantly reduced in the clinical groups in comparison to the healthy controls, indicating an impaired RIF effect in individuals with depression and schizophrenia. A study investigating the different RIF procedures revealed that RIF may be a stable measure over time. However it may not be a heritable aspect of cognition as the study of twin pairs revealed no evidence of a genetic association. RIF was however, found to be associated with smoking status and mood in both patients and controls with a reduction in RIF with low mood and an increase in RIF with smoking status.

These findings confirm that RIF is an important factor in depression and schizophrenia with potential implications for clinical settings. The twin study suggests that RIF is most likely influenced by environmental factors. Indeed modulation of the cholinergic system and mood were found to play a part in mediating inhibitory processes that underlie RIF. These findings have important implications for the theoretical accounts of RIF and the neurochemical bases of inhibitory processes.

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Acknowledgements

I would like to start by thanking my supervisory team; my initial director of studies, Dr David Groome, without whom this research would not have occurred. I particularly want to thank him for the inspiration of ideas and continuous support during his role. A great big thank you to my current director of studies Dr Trudi Edginton who took up the role upon David's retirement and has made a major theoretical contribution to the direction of this work. Trudi's reassurance, support and empathy have contributed to the completion of this work. My second supervisor Dr Kevin Morgan has contributed in securing association with the IOP, provision of testing materials and statistical input. Kevin has provided continuous support throughout and his excellent ideas have made a major contribution. My third supervisor, Professor Angela Clow joined the team upon David's departure. Angela motivated me to structure the write-up and her enthusiasm and appreciation of my work increased my confidence. I am most grateful to all my supervisors for enabling me to work at my own pace, and all their support and encouragement throughout this endeavour.

Staff and PhD students in the psychology department at the University of Westminster have encouraged me throughout the process, and I simply could not imagine a more supportive environment to work and study in. Special mention to: Mark Gardner, Youla Pipilis, Lisa Thorn, Jane O'Conner, and Andrea Oskis for their help in the early stages; Lejla Manzukic-Kanlic, for all the professional and personal support throughout and mostly for encouraging me to have a baby! Maria Flynn, Haulah Zacharia, Dr. Tina Cartwright, Dr. John Colwell and Chantal Gautier for the persistent praise. Dr. Donna Taylor, Nina Smyth, David Barron, Jay McKenzie, Deborah Husbands, Boris Altemeyer and Robin Law for brightening up the PhD

room and being amazing friends. I would not be right not mention Mike Fisher for his very approachable nature, outstanding communication and guidance throughout.

I would also like to thank my family and friends without whose love and support this would not have been possible: my partner, David Bzheta, for adding meaning to my life and his remarkable patience and understanding, our daughter, Isabelle, for being such a brilliant child and positively changing our lives; my parents for providing continuous support and encouragement and being a major help with childcare; my sister, Filomena, for being the most supportive person imaginable in every respect, I cannot thank her enough for all the things that she has done; my brother, Mirad, for never failing to make me laugh and being such an amazing uncle to Isabelle; my wonderful in-laws who have shown love and appreciation throughout; ‘nana’ Martha, (my neighbour) for being like a mother to me and readily available to help at all times; and my friends Lesley and Samantha for cheering me on and believing in me.

Last, but not least, I am grateful to all the participants for taking part and most of all for making data collection an enjoyable experience; all the staff and clients at Havering Mind; all parents at Emblem Youths football club for their support and participation, and Dr. Timothea Tulopoulou and Sheena Owens at the Institute of Psychiatry for the opportunity to work on the twin’s project.

Dedication

This thesis is dedicated to Mr and Mrs Paulin and Liza Sterkaj (my parents); to whom I am very grateful for all the sacrifices made in bringing us to this wonderful country.

Declaration

I declare that all the material contained in this thesis is my own work.

Chapter 1

General Introduction and Background

''A retentive memory may be a good thing, but the ability to forget is the true token of greatness''.

(Elbert Hubbard)

1.1 Introduction

This chapter provides a background into the role of memory retrieval and forgetting in association with schizophrenia and depression. The main theories and research findings are reviewed followed by the rationale for this research and an outline of the main aims and hypothesis of this thesis. A series of studies were conducted investigating a specific inhibitory process known as Retrieval Induced Forgetting (RIF) in schizophrenia and depression. This thesis aims to provide a significant contribution to knowledge by exploring the RIF effect within these disorders in comparison to healthy controls, whilst addressing factors contributing to the mediation of the paradigm, which have largely been ignored thus far.

1.2 Importance of Forgetting

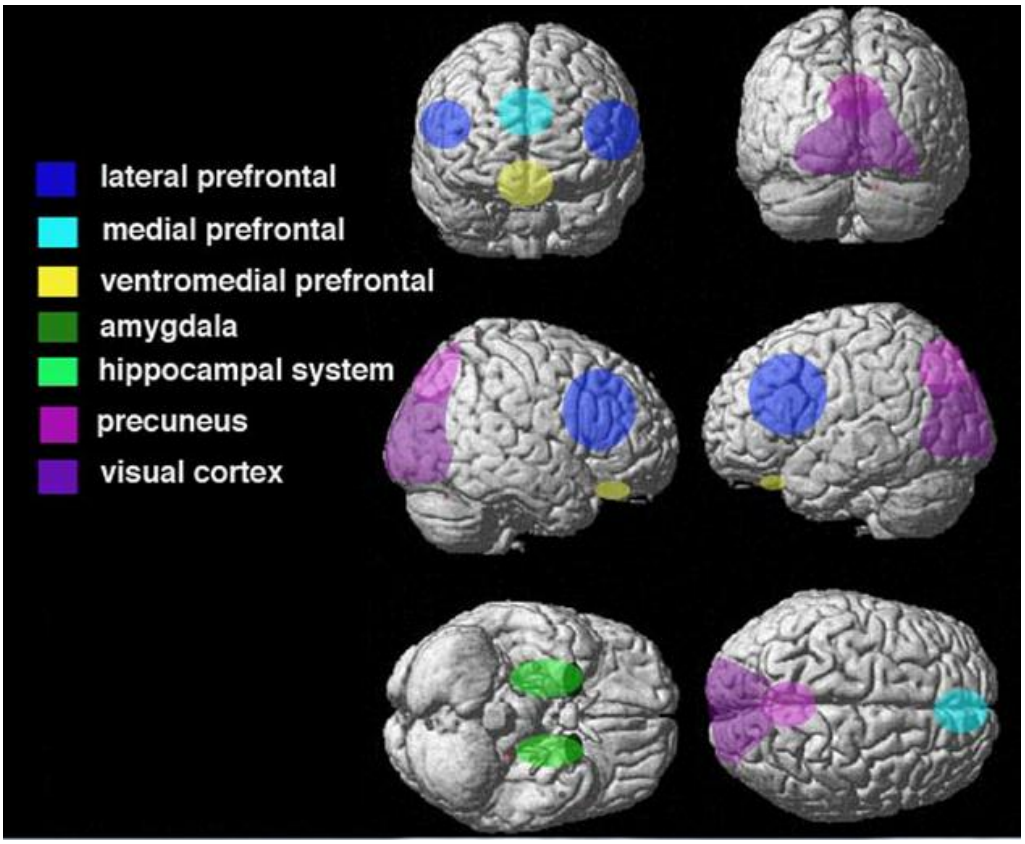
Forgetting is critical for the efficient and adaptive functioning of human memory. Without the ability to inhibit outdated or irrelevant information, humans would become vulnerable to a devastating accumulation of proactive interference, greatly

impeding the ability to learn and access current information (Storm, Bjork, Bjork and Nestokjo, 2006). Research suggests that remembering or forgetting events from the past occurs in a goal-directed, strategic way (Bjork, Bjork, & Anderson, 1998; Conway, 2005). Bjork, et al., (1998) defined goal-directed forgetting as "forgetting that serves some implicit or explicit personal need" (p.103). Despite this definition, forgetting is often equated with failure (Cubelli, 2010), this is probably due the influence of the computer metaphor of human memory, which sees human information processing as a sequence of steps where information is encoded, stored and then retrieved. By this view, recall is expected to be perfect or verbatim, just as a computer can output on command completely and accurately the contents saved in its memory system. However for human memory, this is neither plausible nor functional. Rather, it may be functional to forget certain information that is irrelevant, redundant, out-of-date, damaging, or distressing (Markowistch and Brand, 2010).

Unlike a computer, human memory accumulates events and experiences from one's past and produces what is known as autobiographical remembering and forgetting. This autobiographical memory serves a range of functions, especially in maintaining one's identity (Conway, 2005; Nelson, 2003) and guiding future behaviour (Pillemer, 2003). Autobiographical memories are recollections of specific episodes from the past. Tulving (1972; 1983) suggested that autobiographical memory consists of a division of episodic and semantic memory systems, divided into personal semantic information (i.e., facts about the self, such as knowing where one was born) and

personal episodic information (i.e., unique events, such as remembering a first day of school, Baddeley 1992). Recalling personal semantic information does not depend on retrieving particular experiences, but rather is linked to feelings of “knowing” or familiarity; whilst, recalling personal episodic information requires re-experiencing and recollecting particular past events (Wheeler, Stuss and Tulving 1997) and integrating information from a number of different subsystems (e.g., sensory information, language, emotion, narrative, etc.; Rubin, 2006). Recalling each type of information seems to rely on differential patterns of neural activation (e.g. Maguire, Mummery and Buchel, 2000), see also figure 1 for the brain regions commonly activated during autobiographical retrieval.

Figure 1.1 A schematic of commonly activated regions during autobiographical retrieval, (Cabeza and St. Jacques, 2007)



Tulving (2002) described autobiographical remembering as “mental time travel”, in which the best, the worst, and the everyday occurrences of one’s lives are relived. In the absence of significant disruption, many things from the past can be remembered. However, autobiographical memory is selective and is more likely to facilitate the recollection of events that places one in a good light, supports the current self-image, or promotes ongoing activities. Whilst attempting to forget with varying success memories of experiences that undermine the current self, contradict one’s beliefs, plans, and goals, and increase anxiety or other negative emotions (Conway, M.A. 2005; Conway, M.A. and Pleydell-Pearce, 2000).

Conway, M.A. (2005; Conway, M.A. and Pleydell-Pearce, 2000) proposed the Self Memory System (SMS) to describe the structure of autobiographical memory and the relationship between autobiographical memory and self-identity. In the SMS, people’s knowledge about their lives is organised hierarchically across three levels of increasing specificity: lifetime periods, general events and event-specific knowledge. A specific autobiographical memory is generated by a stable pattern of activation across all three levels of knowledge. However, the construction of this pattern of activation is constrained by executive control processes that coordinate access to the knowledge base and modulate output from it (Conway, 2005;Conwayand Pleydell-Pearce, 2000). These control processes are termed the “working self”. The working self can facilitate or inhibit retrieval of certain memories depending on current goals. In the SMS, goals influence the encoding,

storage, and retrieval of information to determine the content and accessibility of autobiographical memories (Conway, 2005).

Conway, M.A. (2005; Conway, M.A. Singer, and Tagini, 2004) identified two fundamental principles underlying autobiographical memory. The first is “coherence”, which refers to the need to maintain an integrated and consistent sense of one’s life experiences. The second is “correspondence”, which refers to the need for episodic memory to correspond with reality. These principles are not mutually exclusive. Rather, a balance between them is required for a functioning autobiographical memory system. This distinction between coherence and correspondence is not new. Bartlett (1932) emphasised that the purpose of remembering, particularly in a social context, is to share one’s impressions with others, so people are likely to construct and embellish upon their memories rather than generate a strictly accurate representation of what happened.

Conway, M.A. (2005) argued that over time, in long term memory, coherence takes precedence over correspondence. The dominant idea from the SMS is that what is remembered and what in turn is forgotten, is determined by one’s current working self (the image of self any given time). As noted above, autobiographical memories that are consistent with the goals and values of the working self are prioritised for remembering, whereas memories that conflict with the working self are likely to be forgotten (Conway, M.A. 2005; Conway, M.A. and Pleydell-Pearce, 2000; Barnier,

Conway, Mayoh, Speyer, Avizmil, and Harris, 2007). Within the SMS model then, autobiographical forgetting is a goal-directed, executive process, where certain memories are actively gated from consciousness. Irrelevant, upsetting or inconsistent memories with current identity goals are particularly likely to be forgotten.

Research within different traditions and paradigms supports the view that certain kinds of memories are forgotten in apparently goal-directed ways. For instance, diary studies have suggested that whereas people are more likely to forget events about themselves that are negative rather than positive, they are more likely to forget events about others that are positive rather than negative (Thompson, Skowronski, Larsen, and Betz, 1996; Walker, Skowronski, and Thompson, 2003). Also, people tend to organise their life story in terms of well-remembered turning points (Thorne, 2000), and forget events that are inconsistent with their current goals and motivations (Habermas and Bluck, 2000). In the clinical domain, some people with post-traumatic stress disorder deliberately and persistently try to forget memories of their trauma (Brewin, 1998), however intrusive memories also interfere with this process leading to dysfunction. People with functional amnesia forget whole chunks or even their entire autobiographical history following a traumatic experience (Kihlstrom and Schacter, 1995), and people with a repressive coping style (low reported anxiety but high defensiveness) are much more likely to forget negative childhood events than non-repressors and will actively suppress negative life events

whether instructed to or not (Barnier, Levin, and Maher, 2004; Myers and Brewin, 1994).

Three major experimental paradigms of goal-directed forgetting have been designed: retrieval-induced forgetting (Anderson, Bjork, and Bjork, 1994), directed forgetting (Bjork, 1970; Bjork, et al., 1998), and the think/no think paradigm (Anderson &Green, 2001). Directed forgetting is claimed to operate at the level of accessibility, temporarily reducing access to the memory. Retrieval-induced forgetting and think/no-think paradigms are claimed to operate on availability, degrading the memory representation itself (Anderson, 2005). Each of these paradigms have been adopted and extended to explore the functional nature of memory, for example by using emotional words as stimuli or by examining specific clinical populations. Studies of clinical populations are important because it has been suggested that people with certain disorders develop memory biases that can maintain their illnesses; that is, their functional remembering and forgetting becomes dysfunctional (Starr and Moulds, 2006). Therefore in order for a memory system to be efficient and adaptive it requires mechanisms that render desired information more accessible and potentially interfering information less accessible.

1.2.1 Definition and Overview of Retrieval Induced Forgetting

There are a myriad of occasions in which specific memory items are facilitated, while other irrelevant memory information maybe simultaneously inhibited, a process that can occur either intentionally or automatically. The degree of control over these mechanisms in memory becomes most apparent when confronted with memories that are emotionally painful or traumatic. In some cases reliving such affective experiences may be beneficial to a point, as in bereavement (Malkinson, 2001). However, if not eventually brought under control, such memories may repeatedly exceed conscious thresholds, becoming intrusive and ruminative in nature. In some conditions, such as post-traumatic stress disorder (PTSD), retrieval of such memories may cause serious distress and impairment.

In view of their importance for behaviour, processes that are involved in the creation and use of memory, such as encoding, maintenance and retrieval have been extensively researched. However, one memory phenomenon that continues to be contentious is the ability to inhibit the retrieval of specific memories. While the last century has brought about a significant increase in the understanding of how memory information becomes less accessible, exemplified in numerous theoretical accounts of how forgetting occurs, it has focused mainly on processes that are automatic (e.g., interference, decay). Only more recently has cognitive psychology and neuroscience probed into whether controlled aspects of memory apply to the

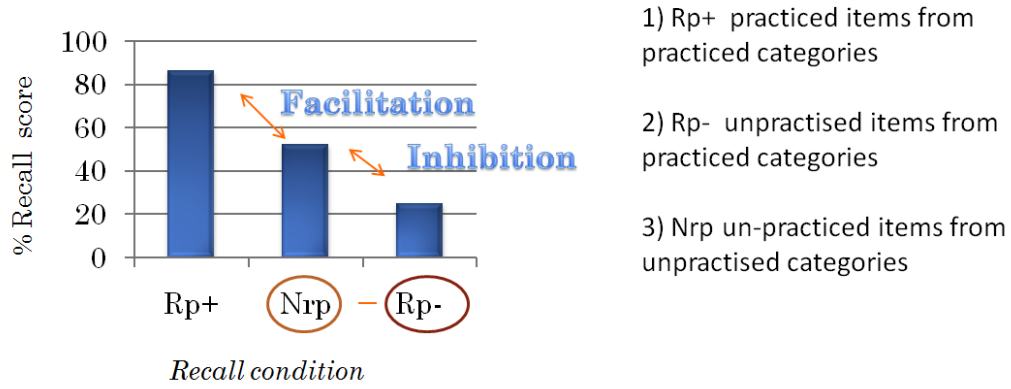
inhibition of retrieval. Consequently, there is little consensus on the specific mechanisms by which control may be exerted to inhibit memory retrieval.

As the focus of this thesis is on the retrieval-induced forgetting (RIF) paradigm a brief overview is provided here then a full discussion is outlined later in this chapter once memory systems are discussed. This is to enable an understanding of the RIF occurrence in context of memory processes. The paradigm was designed by Anderson, Bjork, and Bjork, (1994) it is argued to model the kind of forgetting that occurs unconsciously in response to competition between memories, by practising some memories at the expense of others. For example a woman who thinks of her wedding day, and consistently remembers the things that went according to, rather than contrary to, her careful plans. After repeated retrieval of the things that went right, she is less likely to remember the things that went wrong. It is the act of retrieval that creates a RIF effect as rehearsal alone is not sufficient. Hence, retrieval-induced forgetting avoids cluttering memory with information that is unwanted, redundant or out-of-date.

In the standard paradigm, participants learn a set of category-exemplar pairs, such as “fruit-apple”, “fruit-banana”, “instrument-flute”, and “instrument-violin”. Participants are then presented with the cue “fruit-ap -” a number of times, and practise retrieving “apple” repeatedly when presented with this cue. Finally, participants are presented with the categories (fruit - instrument) and asked to recall all the exemplars for each

one. Typically, participants are less likely to recall “banana” than they are to remember “flute” or “violin”. This is the RIF effect (see Figure 2): retrieval practice reduces recall of unpractised exemplars from the practised category, relative to exemplars from an unpractised category. There is an inhibition effect of Rp- items and a facilitation effect of Rp+ items relative to Nrp items.

Figure 1.2. Graph demonstrating the standard pattern of the typical RIF effect.



It has been suggested that when presented with “fruit– ap -” all the fruit exemplars are activated to some extent, and so successful retrieval practice of “apple” requires the inhibition of the competing, irrelevant fruit exemplar “banana”. This means that “banana” is subsequently more difficult to recall than non-competing irrelevant information (like flute, violin), which was not activated during retrieval practice (Bjork, et al., 1998; Levy, et al., 2010). It has been argued that RIF impairs both memory accessibility and availability. This is supported by evidence showing that recall of unpractised, related exemplars is still inhibited when tested with a novel,

independent cue (Anderson, 2005; Anderson and Spellman, 1995) There is also debate about a non-inhibitory account of this phenomenon (MacLeod, Dodd, Sheard, Wilson, and Bibi, 2003). A detailed account of these processes is provided later in this chapter. Prior to outlining specific inhibitory mechanisms in memory a background of memory systems and processes will be discussed.

1.3 Memory systems and processes

Memory is one of the most fundamental aspects of human existence; advances in research continue to enhance the understanding of its structure and function. Although there is considerable debate, it is generally accepted that memory consists of multiple systems predominantly 'short-term and long term memory' within which there are subsystems. Long-term memory is fractionated into two domains, declarative and non declarative (see figure 3). Declarative, or explicit, memory refers to the ability to consciously recall facts (semantic memory), events (episodic memory), or perceptual information (perceptual memory). Declarative memory allows remembered material to be compared and contrasted; it supports the encoding of memories in terms of relationships among multiple items and events. The stored representations are flexible and can guide performance under a wide range of test conditions.

Declarative memory is representational, it provides a way to model the external world, and as a model of the world it is either true or false. In contrast, nondeclarative memory is neither true nor false. It is dispositional and is expressed through performance rather than recollection. Nondeclarative forms of memory occur as modifications within specialised performance systems. The memories are revealed through reactivation of the systems within which the learning originally occurred. Non declarative memory requires the implicit recall of information and is usually divided into procedural, priming, or simple conditioning paradigms.

Information that is retained on the order of seconds or minutes is usually referred to as short-term memory and is thought to represent a memory system distinct from long-term memory. Short-term memory, refers to the short-term store required to perform certain mental operations during retention. Evidence suggests that short term memory is a passive memory system however active manipulation of material is accomplished by the working memory. Thus short term memory has generally been replaced or is covered under the umbrella term working memory (Goldman-Rakic, 1995; Fuster, 2008).Much of the short-term organisation of behaviour requires some limited memory capacity to support on-line processing, as in the concept of 'working memory' (Baddeley and Hitch, 1974). Equally, there is a need to filter on-going experience and buffer this information so as to organise its efficient entry into long-term memory (Atkinson and Shiffrin, 1971; Waugh and Norman 1965 and Marr 1971)

There has been considerable debate since the 1960's as to whether memory should be regarded as a single unitary system or whether it should be fractionated into two or more subsystems. Evidence in favour of a dichotomy emerged from brain damaged patients (Baddeley, 1990); those suffering from the classic amnesic syndrome appeared to have gross disruption in the ability to form new lasting memories but showed preserved performance on a range of tasks that were assumed to test short-term memory (Warrington, et al., 1970). Conversely, a second type of patient was identified who appeared to show normal long-term learning but had a short-term memory span limited to one or two items (Shallice and Warrington, 1970). It was suggested that such patients had a deficit in short-term storage, in contrast to the long-term storage deficit that occurs in the amnesic syndrome. This finding compared to those of healthy individuals provided evidence for dichotomous theory of memory as proposed by Atkinson and Shiffrin (1968)

Neuropsychological evidence from organic amnesia patients suggesting that there is a double dissociation associated with the hippocampus and related systems, and short-term buffer disorders associated with neocortical damage: amnesic patients present with impaired LTM and preserved STM (Baddeley and Warrington 1970; Drachman and Arbit, 1966) whereas short-term buffer disorders show the reverse pattern (Shallice, 1988). Physiologically, STM is often thought of as maintained neuronal firing (Davelaar, et al., 2005; O'Reilly, et al., 1998) or short-term

potentiation of synaptic connections (Burgess and Hitch, 1999) whereas LTM is thought of as long-term potentiation of synapses (Davelaar, et al., 2005). Generally evidence would suggest that there are clear dissociations between STM and LTM, however each is very important for the other and interaction between STM and LTM is complex (Baddeley 2000; Ranganath and Blumenfeld, 2005).

Working memory is viewed as a comprehensive system that unites various short and long-term memory subsystems and functions (Baddeley, 1986). Diverse working memory theories and models have several structures and processes in common: a division into verbal and visual-spatial stores; an encoding function; involvement in effortful retrieval from long-term memory; enactment of strategic processes; and executive and attentional processes. In general, the combination of moment-to-moment awareness, efforts to maintain information in short-term memory, and the effortful retrieval of archived information constitutes working memory.

Working memory capacity (WMC) is related to the ability to control attention, particularly under conditions of interference or distraction (Engle and Kane, 2004). Importantly, in many situations in which cognition and behaviour can be controlled under conditions that do not include distraction or interference, there are no differences in performance as a function of WMC (Kane, Bleckley, Conway, A.R.A. and Engle, 2001; Kane and Engle, 2003). Data have generally supported the

controlled attention framework, and suggest that control is particularly important in situations that place a premium on active maintenance of task goals in the face of distraction, or require the retrieval of information under conditions of response competition (Conway, A.R.A. and Engle, 1994; Unsworth and Engle, 2007).

Many real-life problems require coordinated and simultaneous encoding and or retrieval of different memories across multiple systems and integration of information with representations of recent experiences and abstract rules in order to solve these problems in an efficient manner. The effortful cognitive processes required under these conditions include selective allocation of attentional resources and manipulation of multiple forms of information processed by different memory systems. In addition, novel or unexpected changes in rules or reinforcement contingencies may necessitate the suppression of memories processed by one system, in order to permit learning managed by other systems to optimise behaviour (Baddeley, Eysenck and Anderson, 2009). These types of cognitive operations are known as facilitatory and inhibitory processes that underlie memory, attention and executive processing.

A plethora of studies have shown that WMC, is related to higher-level cognition, including measures of episodic memory (Kane and Engle, 2000; McCabe and Smith, 2002; McCabe, Smith, and Parks, 2007; Park, Lautenschlager, et al., 2002; Park,

Smith, et al., 1996), reasoning (Barrouillet, and Lecas, 1999; Kyllonen and Christal, 1990), reading comprehension (Daneman and Carpenter, 1980; Lustig, May, and Hasher, 2001), and fluid intelligence (Engle, et al., 1999; Colom, Rebollo, Palacios, Juan-Espinosa, and Kyllonen, 2004). Executive function encompasses a variety of higher cognitive processes that use and modify information from many cortical sensory systems in the anterior and posterior brain regions to modulate and produce behaviour (Goethals, et al., 2004; Fuser 1999). These integrative functions include both cognitive and behavioural components that are necessary for effective, goal-directed actions and for the control of attentional resources, which are at the basis of the ability to manage independent activities of daily living (Lezak, 1995; Stuss and Levin 2002).

1.3.1 Executive control and attention

Executive function includes control functions related to the inhibition of prepotent responses, shifting mental sets, monitoring and regulating performance, updating task demands, goal maintenance, planning, working memory, and cognitive flexibility, among others (Baddeley, 2012; Banich, 2009; Lezak, 1995; Fuster, 1997). Executive control and the mechanisms of retrieval actions, once started, can usually be stopped. This is sometimes referred to as response override, and in response override, one must stop a prepotent response to a stimulus (such as a falling object). This governed by working memory, its main mode of operation is assumed to be that

proposed by Norman and Shallice (1986), who assumed two modes of control, one of which is automatic and based on existing habits whereas the other depends on an attentionally limited executive.

Driving a car would be an example of the first type of semi-automatic control. The activities involved can be relatively complex, so that potential conflicts can occur, for example between continuing to drive and slowing down in response to a traffic signal, or another driver entering the road. These are assumed to be well learned procedures for resolving such conflicts automatically because such behaviour is based largely on well learned habits and thus require little attention. However, when automatic conflict resolution is not possible, or when a novel situation arises, for example if a road is closed for repairs, then a second system is called into action, the supervisory attentional system (SAS). This is able to intervene, either in favour of one or other of the competing options or else to activate strategies for seeking alternative solutions. It is the SAS component that is assumed to be crucial and integral or comparable to the central executive (Baddeley, 2012).

Executive Function is associated with the frontal lobes and related brain networks. The area of the prefrontal lobe and, in particular, the dorsolateral prefrontal cortex (DLPFC) and the cingulate cortex (the anterior cingulate) have been related to the cognitive aspects of EF (Stuss and Levin, 2002). Patients with frontal damage

frequently display impairments in cognitive functions attributed to EF, although activation of other brain areas, such as the parietal lobe, association areas and sub-cortical areas, including the limbic areas, are also attributed to EF (Lezak, 1995; Stuss and Levin 2002; Collette, et al., 2006). In general, the anterior parts of the frontal lobes are involved with aspects of self-regulation, such as inhibition and self awareness, whereas the dorsal parts are involved with reasoning processes.

Neuroimaging studies attempting to localise the activity of EF report inconsistent findings. Collette, et al., (2006) reviewed investigations that explored the neural substrates of EF, focusing on specific aspects, such as response inhibition and dual task coordination. They found that different EF tasks not only activated different frontal and parietal areas, they also activated other areas of the brain. This supports the hypothesis that EF is based on a network of anterior and posterior cerebral areas and is not localized only to the frontal cortex. Stuss and Alexander (2000) argued that the common use of the term “frontal function” (or “frontal syndrome”) as a synonym for EF is not accurate, because of the many methodological problems in the majority of studies that have tried to explore associations between the two. In support of that claim, a meta-analysis found that three classical tests of EF, the Wisconsin Card Sorting Task, the Stroop Task, and verbal fluency tasks (Alvarez and Emory 2006) were sensitive to frontal lobe damage, but other areas of the brain could also lead to poor performance in these tests. The authors suggested that the

frontal lobes participate to a greater extent than other areas of the brain in functions considered to be executive.

Another important aspect in executive function is, attentional control, attention may be considered a specific example of EF (Stuss and Levin 2002). The term covers a number of different processes that are related aspects of how the organism becomes receptive to stimuli and how it may begin processing incoming or attended-to excitation, whether internal or external. There is, however, “no single and clear-cut definition of attention. Posner, et al., (2006) view attention as an anatomical network whose primary purpose is to influence the operation of other brain networks. Attention can be classified into separate functions, including focused or selective, sustained, divided and alternating, although these distinctions are somewhat artificial (Rogers 2006). Selective attention, which enables filtering of stimulus information and suppression of distracters, is commonly referred to as “concentration’’ (Lezak 1995). Sustained attention refers to the ability to maintain attention to a task over a period of time.

Divided attention refers to the ability to carry out more than one task at the same time and alternating attention refers to rapid shifting of attention from one task to another (Rogers 2006).The attention attributed to a stimulus in turn determines the memory formed, and how these are later accessed. It is generally assumed that

there are two distinct ways of gaining access to past experiences: recollection of contextual details surrounding a previous encounter with a stimulus (source-memory), and a general sense of familiarity that is sufficient to determine whether the stimulus was previously encountered in the absence of contextual recollection (item memory) (Atkinson and Juola, 1974; Banks 2000; Clark and Shiffrin 1992; Dobbins, et al., 2000 and Tulving, 1985).

Item memory combined with source memory failure is a common experience in everyday life and plays an important role in such problems as faulty eyewitness identification, when a face perceived as familiar is assigned the wrong source context (Schacter, 2001). Although it has been demonstrated that recall requires greater processing capacity than recognition (Whiting & Smith, 1997), few studies have considered working memory development from the standpoint of executive processing demand. Recent work supports the notion that the basic modular structure of working memory (according to the Baddeley and Hitch, 1974, model) is present from age 6 years onward and that each tripartite component of the model increases its capacity until early adolescence (Gathercole, Pickering, Ambridge, and Wearing, 2004).

1.3.2 Neuropharmacology of memory and executive function

Interest in the development of the prefrontal cortex has intensified in recent years, because the prefrontal cortex orchestrates high-level cognitive functions that support responsible adult behaviour. Among these functions are inhibitory control (Diamond, 1990), the ability to integrate past knowledge with future goals (Fuster, 1997), and behavioural flexibility (Dias, Robbins, & Roberts, 1996). It is presumed that in healthy individuals these functions interact cooperatively to promote adaptive future-directed behaviour. Future-directed behaviour is by definition integrative. It requires that one is able to represent pertinent information in mind, ignore extraneous distractions, and translate goal-related representations into behavioural actions at appropriate times, using recall to guide those actions. It is often assumed to require working memory. Theories of cognitive control typically include an executive component that is responsible for coordinating goal-directed behaviour (Baddeley and Hitch, 1974; Balota, Law, and Zevin, 2000; Braver, Gray, and Burgess, 2007; Engle and Kane, 2004; Hasher and Zacks, 1988; Jacoby, Bishara, Hessels, and Toth, 2005; Logan, 2003; Miyake, et al., 2000; Posner and DiGirolamo, 1998; Shallice and Burgess, 1993).

Similar prefrontal regions appear to be activated by spatial working memory tasks (i.e., the spatial n-back; see Nelson, et al., 2000) in prepubertal children as compared with young adults (Nelson, et al., 2000; Thomas, et al., 1999). There are

few comprehensive studies that have assessed working memory and cognitive control processes in adolescents between the ages of 12 and 20 years. The frequently cited conclusion that these functions reach maturity during adolescence is largely derived from studies such as the Welsh, et al., (1991) and Luciana and Nelson (2002) studies that report performance differences between prepubescent children and young adults. A recent study (Luna, Garver, Urban, Lazar, and Sweeney, 2004) used oculomotor working memory and cognitive control tasks to demonstrate continued development of processing speed, working memory, and inhibitory control from late childhood to young adulthood. Additional knowledge is derived from neuroimaging investigations that reveal several brain changes occurring during adolescence. These changes are important to describe because they suggest that improvements in executive control are presumed to be prefrontally mediated in adults and that they continue to develop into early adulthood.

Sowell, Delis, Stiles, and Jernigan (2001) reported that frontal gray matter decline predicted delayed verbal memory performance and visuospatial memory in 35 children ages 7 to 16 years. In addition, functional neuroimaging studies suggest that changes in prefrontal cortical activity and metabolism might underlie working memory improvements. For instance, Klingberg, Forssberg, and Westerberg (2002) measured brain activity in fourteen 9to 18yearolds while they performed a spatial delayed recognition task under low versus high memory load conditions. They

reported activation in superior and middle frontal regions, as well as regions of the parietal lobe, that increased with age and working memory capacity. Similarly, Kwon, Reiss, and Menon (2002) reported age-related increases in prefrontal cortical activation associated with visuospatial two-back performance in a small group of twenty-three 7- to 22-year-olds.

Mounting evidence from human imaging and animal studies suggests that different regions of the PFC play a key role in retrieval of content from long-term memory (Wickens, et al., 1996; Calabresi, et al., 1999, Centonze, et al., 2001; Bissière, et al., 2003; Park, et al., 2004). In the past 10 years, fMRI studies have showed increased activation of prefrontal networks (in particular, the lateral PFC), during retrieval of different types of memories. These include semantic (Mitchell and Johnson, 2009), episodic (Lee, et al., 2000) emotional (Buchanan, 2007), and rule-related (Bunge, 2004) memories. Although central to understanding the cognitive and neural computations subserving source retrieval, the nature of these reflective processes and their selectivity to recollective, as opposed to familiarity-based, memory remains largely unknown. Contrary to the reflective hypothesis, alternative accounts contend that left ventrolateral PFC activation results from the successful retrieval of episodic details or operations contingent upon retrieval success (Henson, et al., 1999 and Konishi, et al., 2000).

Encoding and retrieval is orchestrated by the medial temporal lobe (MTL), a major terminus of the various sensory processing pathways. As the neuronal firing of these sensory features is maintained by focused attention on the representation of a stimulus, a binding process occurs within the hippocampus proper and its surrounding MTL cortices (parahippocampal and entorrhinal cortices) to conjoin the different perceptual features of the event (Jonides, et al., 2008 and O'Reilly and Norman, 2002). Within the hippocampus, this process occurs in a sparse neuronal firing pattern that is thought to index and represent the original neural representations of the event that occurred in various sensory processing regions. By encoding and binding these conjunctive representations into a sparse representation in the hippocampus, the likelihood of interference from other events is decreased. The hippocampus proper exhibits a fast learning rate, which also minimizes interference that may occur during the time between perception and encoding (O'Reilly and Norman, 2002 and O'Reilly and McClelland, 1994).

Plasticity begins to occur as the hippocampus starts binding these different neural sensory representations of the external event (Hebbian and non-Hebbian LTP). Asplasticity takes place, causing increased communication between pre- and post-synaptic cells associated with the sparse representation. This process allows the linkage between the different neural sensory component representations of the specific event within the hippocampus proper via enhanced protein synthesis

(Wixted, 2004 and Jonides, et al., 2008). The plasticity process provides the neural mechanisms of consolidation, in which a particular external event becomes a lasting memory, which is the basis for long-term memory (LTM).

If encoding occurs with sufficient activation during a specific event, a memory may become established and durable. If so, then a particular internal or external sensory cue may facilitateretrieval. The memory of the initial event is retrieved through activation of one of the component representations in the neural network that represents the entire composite memory representation. Specifically, if a component representation is activated and attention is focused on it, the representation may then continue to activate in a feed-forward manner to the hippocampus. If this occurs, activation of any linked component representation of the original event in sensory regions may feed-forward to the hippocampus, causing the sparse representation indexed within the hippocampus to pattern complete (Depue2012).

Pattern completion then reactivates all the specific component representations of the original event through feed-back activation from the hippocampus to sensory regions that originally encoded the event. Although there is recent evidence that the hippocampus is not always required (Aggleton, 2012). As more attention is focused on the emerging component representations of the features of the original memory event, the specific representations which were first engaged in perception are

reactivated to some degree. Attentional resources (prefrontal and parietal regions) then maintain the firing of these representations as a composite memory (Jonides, et al., 2008).

The maintenance of these retrieved memories is thought to be governed by a cortical-basal ganglia-thalamo-cortical loop. In this loop sensory representations in posterior cortex are actively maintained by the prefrontal cortex (PFC) through a gating mechanism in the basal ganglia and thalamus that allows the PFC to communicate with posterior cortex (Frank, et al., 2001and Hazy, et al., 2006). This gating mechanism is controlled by dopaminergic input to the basal ganglia and signals when to open and close the gate so that PFC can flexibly maintain the firing and updating of memory representations. During maintenance, the flow of information is inhibited so that current representations that are actively firing in PFC can continue to do so. Conversely, when updating occurs this loop becomes uninhibited, so that new information can transfer to the PFC for subsequent maintenance (for a review see O'Reilly and Frank, 2006). The selective maintenance and updating of these representations is the basis for which information is accessible to working memory (WM) and ultimately what is recalled.

Inhibition of retrieval can be influenced by differences in the nature of processing for example automatic or controlled processes. While both automatic and controlled

processes can be seen as essential for effective memory function, they likely involve different neural components. Automatic processes occur outside of awareness or cognitive influence, whereas controlled processes are cognitively directed (Depue, 2012). Automatic processes are more akin to conceptions of standard processes of forgetting for example proactive, retroactive and interference. Inhibition of retrieval implies a cognitively directed mechanism to lessen the accessibility of memory information. There are three main hypotheses that define the manner in which inhibition of retrieval may occur. Although these hypotheses have not been fully specified in mechanistic detail in the literature, they do encompass the major competing views about how inhibitory modulation may reduce or lessen memory retrieval. Also Edginton and Rusted (2003) provided further evidence for inhibitory processes in the RIF paradigm arguing for a more complex subdivision of inhibitory processes, which may be differentially influenced by cholinergic blockade. The authors also found that nicotine, via cigarette smoking, is a modulating factor in RIF as they reported that nicotine can affect task performance by inhibiting unpractised material thereby reducing interference and benefiting the task at hand.

Retrieval Induced Forgetting is thought to be driven by direct inhibition (Anderson, Bjork and Bjork 1994), which is the idea that retrieval inhibition or directed suppression causes inhibition over a specific, singular memory representation (Geiselman, et al., 1983, Bjork, 1989, Bjork, et al., 1998, Anderson and Green,

2001 and Levy and Anderson, 2002). According to this hypothesis, as cues relevant to stored memories are accessed or maintained by WM, the cues initiate cognitive control processes exerted by PFC. The PFC is hypothesised to send an inhibitory signal directed at the specific representation of the target memory, stored as a long-term memory that has been associated with the cue, thereby preventing retrieval (Anderson, 2011).

Cognitive theory and neuropsychological evidence suggest at least two controlled operations that might be more involved in source memory than item memory (Burgess and Shallice 1996; Moscovitch and Melo 1997; Schacter, et al., 1998 and Tulving 1983). The first is retrieval cue specification, which is the systematic analysis of the possible semantic relations between the retrieval cue and the known characteristics of the potential sources. The second operation especially important for source memory is recollection monitoring, which is the process of evaluating the products of memory retrieval with respect to their relevance to the retrieval task. Unlike simple item recognition tests, where participants can endorse items based on simple familiarity, participantsmay recollect information during source tasks that varies considerably in its task relevance and must therefore evaluate retrieved recollections to determine their current task relevancy (Dobbins, et al., 2002).

Recent neuroimaging work suggests that these functions may be localised in discrete parts of the prefrontal cortex (Maller, et al., 2010). As discussed the role played by PFC in a variety of executive functions is well established (Fuster, 2008), damage to the frontal lobes leads to impairments on tasks that require different aspects of executive functioning, such as selective attention, working memory, and behavioural flexibility. It is widely accepted that to affect overt changes in ongoing behaviour, information processed by the PFC interfaces with the motor and motivational systems via descending connections to the basal ganglia (Florensco and Jenstch, 2012).

Different tasks designed to isolate specific executive processes engage common regions of localised activation (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). This evidence suggests that specific executive mechanisms entail fundamental and dissociable processes that may be shared among different cognitive tasks. Executive processes may be susceptible to behavioural interactions between tasks. Such interactions could involve negative or positive transfer between tasks that are presumed to involve the same executive functions. There is evidence for both types of transfer effects, for example, working memory (Klingberg, Forssberg and Westerberg, 2002), inhibitory control (Dowsett and Livesey, 2000), and dual-task management (Kramer, Larish and Strayer, 1995) can be enhanced by extensive training over days and weeks, and training effects can transfer to other

tasks thought to involve similar executive processes. Conversely, intensive performance of one or more complex tasks involving multiple executive processes can subsequently result in reduced performance on other tasks presumably sharing these executive processes (e.g., Van der Linden, Frese, and Meijman, 2003). Such cognitively challenging tasks are presumed to cause cognitive fatigue or resource depletion (Parasuraman, 1998; Wickens, 1984) thereby compromising performance on other tasks that require the same executive resources (Engle, Conway, A.R.A. Tuholski, and Shisler, 1995; Vohs and Heatherton, 2000).

Experimental and clinical studies have shown the involvement of the cholinergic system in cognitive functioning in animals and humans. Structural lesions to cholinergic basal forebrain neurons or application of muscarinic and nicotinicacetylcholine (Ach) receptor antagonists leads to impaired memory performance and changed behaviour (Damasio, et al., 1985, Decker and McGaugh, 1991, Newhouse, et al., 1994 and Vitiello, et al., 1997). However cognitive decline is associated with healthy aging, specifically age-related decline in episodic memory has been linked to a decline in cholinergic function which may be associated with inhibitory processes (Edington and Rusted 2003, Bishop, et al., 2010). Indeed there is evidence that the cholinergic replacement therapy in Alzheimer's disease (AD) patients using ACh receptor agonists

oracetylcholinesterase (AChE) inhibitors improvecognitive efficiency in some individuals (Buccafusco and Terry, 2000).

There is also evidence that cholinergic and dopaminergic transmission, clearly play a role in attentional performance. For example, lesions of the basal forebrain cholinergic system, or cholinergic deafferentation in the PFC, impair attentional performance (Muir, et al., 1994; McGaughy, et al., 2002), and these effects are attenuated by the administration of acetylcholinesterase inhibitors (Muir et al, 1992, 1995; Balducci, et al., 2003). Impairments in attentional accuracy induced by cholinergic lesions may be due, in part, to reduced muscarinic transmission, as systemic blockade of these receptors with scopolamine, a muscarinic antagonist, impairs performance on the five-choice serial reaction-time task (5-CSRTT) (Mirza and Stolerman, 2000). A large body of work shows that systemic administration of nicotinic receptor agonists (including nicotine itself) produces their clearest and most robust performance enhancements in signal detection or choice reaction time tasks. Specifically, acute treatment with nicotine increases choice accuracy and speeds response times in both tests (for comprehensive reviews see Heishman, 2000; 2010).

Nicotine is a cholinergic agonist, and has been extensively used as a tool for exploring the modulatory role of cholinergic activation in human cognitive performance. Positive effects of nicotine administration have been reported in a number of comprehensive reviews. Nicotine has been found to reliably improve measures of attention in both habitual smokers and also in nicotine-naïve volunteers.

Effects on memory processes, though less robust, have been reported under conditions that stretch cognitive resources or require strategic processing of the to-be-remembered material (Heishman, et al., 1994; Foulds, et al., 1996; Rezvani and Levin 2001; Levin, et al., 2006). More recent formulations of memory processes, however, highlight the crucial role of inhibitory mechanisms in the process of efficient remembering (e.g., Schacter 2001; Miyake, et al., 2000; Friedman and Miyake 2004). That is, the suppression of irrelevant information is key to the effective processing of relevant material.

Although the neurochemistry of inhibition processes has not been widely researched, recent studies, using the retrieval-induced forgetting paradigm have demonstrated that nicotine increase inhibition. Providing evidence for cholinergic modulation of inhibitory processes in the RIF paradigm adding to the understanding of neurochemical mechanisms underlying human information processing (Edginton and Rusted 2003). Further studies have reported positive effects of nicotine on the ability to inhibit task-irrelevant semantic information, off-target saccades and prepotent prosaccades, respectively (Rycroft, et al., 2005; Rycroft, et al., 2006). Rusted and Alvares (2007) argued that pharmacological manipulation of RIF relate to the direct modulation of information processing by nicotine.

1.4 Selective Retrieval and the Retrieval Induced Forgetting Paradigm

When recalling a memory, the desired trace is rarely the only memory related to the cues guiding retrieval. Most cues are related to many memories, and very often, non-target memories are more strongly associated to the cue than is the currently desired trace. In this situation, the associated traces compete for access to conscious awareness, necessitating some process to enable selective retrieval (Anderson and Levy 2003). In their framework, selective retrieval represents a paradigmatic case of response override, where one must select a weaker memory in the face of interference from one or more proponent competitors. The authors argued that if stopping prepotent responses engages inhibition, the same mechanisms might also be engaged to stop prepotent memories from coming to mind, promoting selective retrieval. If so, perhaps inhibition will induce long-lasting memory impairment for the competitors. Thus, the very act of retrieval should cause forgetting of related memories. This prediction has been explored in a procedure known as the retrieval practice paradigm.

This retrieval practice paradigm is argued to measure the unconscious suppression of memories and was designed to investigate the nature of inhibition in memory. As mentioned in the opening paragraphs of this chapter participants in these studies are not instructed to forget anything. On the contrary, they are requested to remember as much as possible. In a typical version of this paradigm participants study a list of category–exemplar pairs in the initial phase (e.g. fruit–orange). Secondly,

participants are cued to recall half of the exemplars from half of the presented categories by means of a category plus word stem cue (e.g. fruit - or). The percentage of correctly recalled items for this phase is important in order to be able to establish that the mechanism which derives RIF was successfully completed, thus ensuring retrieval.

The consequence of this retrieval practice phase is that three subsets of item are created: practiced items (Rp+ items), items that belong to the practiced category, but are not practiced for (Rp- items), and items which were not practiced and belong to an un-practiced category (Nrp items). Thirdly, after a retention interval (between15 to 20 minutes), the final phase of the paradigm is conducted: participants are presented with all the studied category names and they are asked to recall as many exemplars as possible from each of the presented categories. As one would expect the recall of the practised exemplars (Rp +) is better than the baseline exemplars (Nrp). Strikingly it is the impaired recall of the non-practised competitors (Rp −) relative to the baseline exemplars (Nrp) that is the key finding, which has become known as “retrieval-induced forgetting” (Anderson, et al., 1994).

Anderson, et al., (1994) demonstrated that the probability of recalling the Rp- items was significantly lower than the probability of recalling the Nrp items, that is, retrieval of some members of the category (Rp+) had the effect of reducing the probability of recalling the unpracticed members of that category. They also claimed that inhibition

of competing memories was the mechanism producing the RIF effect: during the retrieval practice phase, Rp- items are inhibited to reduce their competing effects and to facilitate recall of the Rp- items. It is the effect that retrieving memories have on related memories that unintentionally and unconsciously causes inhibition (Dehli and Brennen 2009).

This finding has been demonstrated by a large number of subsequent studies (Shaw, Bjork and Handal, 1995; Ciranni and Shimamura, 1999; Anderson, Bjork and Bjork, 2000; Bauml and Hartinger, 2002; MacLeod, 2002; Perfect, Conway, M.A. Moulin and Perry, 2002; Edginton and Rusted 2003; Barnier, Hung and Conway, 2004; Groome and Grant, 2005; Groome, Thorne and Grant 2007, and Groome and Pipilis, 2007; Groome and Sterkaj 2010;). The results of these studies consistently show that retrieval practice not only facilitates recall of the practised items, but it also inhibits the recall of related items. This detrimental effect of retrieval referred to as retrieval-induced forgetting (Anderson, et al., 1994) occurs on tests of both episodic and semantic memory (Bäuml 2002; Johnson and Anderson 2004) and has proven relevant in a variety of settings such as eyewitness memory (Shaw and others 1995; MacLeod 2002), false memories (Bäuml and Kuhbandner 2003; Starns and Hicks 2004), impression formation (Macrae and McLeod 1998), and stereotype representation (Dunn and Spellman 2003; Quinn, et al., 2004).

Clinical disorders such as depression and schizophrenia are known to be associated with a number of cognitive abnormalities particularly within memory and executive functioning. RIF inhibitory processes have not been investigated for their role in sustaining or perhaps even contributing to depression and schizophrenia. Other retrieval abnormalities include over-selective memory with a bias to retrieval of distressing events (Bower 1981, Rusting and Dehart 2000), over-generalised retrieval (Williams 1999), and excessive rumination (Nolen-Hoeksema 2000, 2006). It is possible that these retrieval abnormalities may be associated with deficits in cognitive inhibition. Since the mechanism underlying RIF is believed to depend on such an inhibitory process (Anderson 2003), there is a possibility that RIF and other related measures of cognitive inhibition may be involved in these memory abnormalities. The role apparently played by RIF in suppressing unwanted memories raises the possibility that the RIF mechanism could also play a part in suppressing distressing intrusive thoughts, which are a feature of many psychiatric disorders and are thought to play a role in contributing to or exacerbating those disorders (Lang, et al., 1999).

Prior to addressing the purpose of this study it is necessary to understand the theoretical background of this memory phenomenon. The principal theories that provide an explanation for the occurrence of RIF will be outlined below followed by

the potential confounding issues associated with the methodologies employed as well as contributory factors that may either facilitate or inhibit this process.

1.5 Theoretical perspectives on Retrieval Induced Forgetting

1.5.1 Outline of Inhibition Theory

Retrieval-induced forgetting has been attributed to inhibitory control mechanisms that are recruited to overcome interference caused by competing memory traces (Anderson, et al., 1994; Anderson and Spellman 1995; Anderson 2003). Inhibition theory argues that RIF is explained by the inhibitory mechanisms active in the retrieval practice phase occurring between study and test, resulting in a temporary deficiency in one's ability to retrieve material stored in memory. In general, successful memory retrieval is assumed to depend on the interaction between an externally provided or internally generated cue and stored memory traces (Tulving 1983). When a cue is associated with several traces, selective retrieval of the desired memory is facilitated by inhibiting other memory traces associated with the same cue, thereby attenuating the interference caused by these competitors. Thus, efficient retrieval practice with category-plus-stem cues (e.g., fruits-or____) would entail inhibition of category exemplars that fail to overlap with the provided stems, which ultimately makes these unpractised exemplar traces less accessible in the ensuing recall phase.

Support for such an inhibitory account of retrieval-induced forgetting comes from work showing that items remain inaccessible in tests using independent probes as retrieval cues (Anderson and Spellman 1995; Anderson 2003; Aslan and others 2006; Saunders and MacLeod 2006). Also studies demonstrating the enhancing effects of nicotine on RIF provide evidence for an inhibitory account (Edgniton and Rusted, 2003; Rusted and Alvares 2007). It is also consistent with work showing that retrieval practice affects only unpractised items' recall accuracy (Bäuml, et al., 2005).

A study employing electrophysiological measures of brain activity provided further support to an inhibitory control account of retrieval-induced forgetting. It was demonstrated that prefrontal regions play an important role in the selection and maintenance of relevant memory representations at the expense of those currently irrelevant (Johansson, Aslan, Bäuml, Gabel and Mecklinger, 2007). In addition the fact that forgetting occurs over a wide range of memory tests, including tests of word stem completion (Anderson, et al., 1994, 2000; Anderson and McCulloch 1999; Bäuml and Aslan 2004), tests of recognition memory (Hicks and Starns 2004; Starns and Hicks 2004), implicit memory tests (Perfect and others 2002; Veling and van Knippenberg 2004) suggests that similar inhibitory processes underlie each construct.

1.5.2 Outline of Interference Theory

The main assumption in the response competition hypothesis of forgetting is that retrieval failures occur because other unwanted memories are retrieved instead of

the target memories. When two different responses are learned for the same stimulus, one may block the other. Thus, two stimulus-response associations are learned independently, but one dominates at the time of retrieval (Crowder, 1976, Anderson, 1983; McGeoch, 1942; Mensink and Raaijmakers, 1988). The idea is that retrieval practice strengthens a subset of items associated to a particular cue, thus blocking or making it more difficult to retrieve other items given that cue—even when output interference is controlled. If retrieval-induced forgetting is the consequence of strength-based associative interference, then the extent to which Rp– items are forgotten should be directly related to the extent to which Rp+ items are strengthened.

1.5.3 Evidence and critical approach of RIF theories

One problem for this account, however, is that retrieval-induced forgetting has been shown to be largely independent from the strengthening of practiced items. For example, when a subset of items are re-presented for additional study instead of retrieval practice, this extra study results in comparable strengthening of target items but typically fails to cause non-strengthened items to be forgotten (Ciranni and Shimamura, 1999; Anderson, et al., 2000,Bäuml, 2002; Saunders, et al., 2009). Similarly, a variety of manipulations including dividing attention (Ortega, Gómez-Ariza, Román, and Bajo, 2012; Román, Soriano, Gómez-Ariza, and Bajo, 2009), inducing stress (Koessler, Engler, Riether, and Kissler, 2009), inducing negative mood (Bäuml and Kuhbandner, 2007), and re-exposing items between retrieval

practice and the final test (Storm, et al., 2008) selectively disrupt retrieval-induced forgetting without influencing the strengthening of practiced items.

These and other observations have shown that retrieval-induced forgetting can be selectively diminished while preserving both retrieval-practice performance and the strengthening of Rp+ items. This pattern of results poses a serious challenge for interference accounts that predict that strengthening and forgetting should be intimately related. Not only is strengthening Rp+ items insufficient to cause forgetting, it also appears to be unnecessary. Normal levels of retrieval-induced forgetting are observed when retrieval practice is made impossible, thus ensuring that participants fail to retrieve anything during retrieval practice (Storm, et al., 2006; Storm and Nestojko, 2010).

In fact, three experiments have directly compared possible and impossible retrieval practice, and none have found possible retrieval practice to cause more retrieval-induced forgetting than does impossible retrieval practice. This finding is difficult to explain by an interference-based account but is entirely consistent with the inhibitory account. Regardless of whether or not retrieval eventually succeeds, if competition is experienced during retrieval, then the competing items should be targeted by inhibition, and as a consequence, they should suffer retrieval-induced forgetting.

1.6 Relevance of Retrieval Induced Forgetting

Bjork (2011) argued that remembering and forgetting reflect fundamentally interdependent processes in human memory. This interdependency is particularly apparent in research on retrieval-induced forgetting. As discussed above one prominent theoretical account holds that retrieval-induced forgetting is caused by an inhibitory process that acts to resolve competition during retrieval. Specifically, when cues activate competing, contextually inappropriate responses, those responses are claimed to be inhibited in order to facilitate the retrieval of target responses (Levy and Anderson, 2002; Anderson 2003; Storm, 2011).

Research has argued that for the concept of inhibition to be accepted as a useful construct in understanding cognition, it is critical for it to be explicitly defined (Storm and Levy 2012). Bjork (1989, p. 324), referred to inhibition as a "suppression-type process directed at the to-be-inhibited information for some adaptive purpose." In this stronger sense, inhibition is a functional mechanism that acts with the specific and direct purpose of reducing the accessibility of an item or items in memory, and an item is said to be inhibited if it is less recallable as a consequence of such a mechanism. In an extensive review of retrieval-based inhibition, Anderson (2003) argued that retrieval is one of many situations in which executive control processes are recruited to override prepotent or interfering responses. He argued that retrieval-induced forgetting is not the consequence of competition or interference per se, but

rather is the consequence of control processes that help overcome competition and interference. In the context of the retrieval-practice paradigm, inhibitory control is recruited during retrieval practice in order to resolve competition by inhibiting the non-target Rp– items, and thus to facilitate the recollection of the target Rp+ items.

Anderson identified several properties that appear to uniquely support the inhibitory account of retrieval-induced forgetting (i.e., cue independence, retrieval specificity, interference dependence, and strength independence), each of which is discussed in more detail below. One of the key characteristics of Anderson's account is that Rp– items are inhibited at the level of their representation. According to this view, retrieval-induced forgetting is caused by the direct inhibition of Rp– items and not by damaging particular cue–response associations (Bjork, Bjork, and Anderson, 1998; Levy and Anderson, 2002; Anderson, 2005; Bäuml, Pastötter, and Hanslmayr,2010; Storm, 2011; Verde, 2012). Studies of such processes in depression and schizophrenia have revealed that patients demonstrate a deficiency in this domain in comparison to healthy controls (Moulin et, al., 2002; Groome and Sterkaj, 2010; Bajo Soriano, et al., 2009, 2012). This suggests that this mechanism may be crucial in understanding the specific function among these disorders.

Although the terms retrieval-induced forgetting and inhibition are often used interchangeably, they have very different meanings. Retrieval-induced forgetting refers to the empirical phenomenon that retrieval causes non-retrieved items to become less recallable; it does not specify the mechanism driving the retrieval process by which the non-retrieved items become less recallable. Depending on the particular methods used or the populations studied, multiple factors can contribute to forgetting (e.g., response competition, strategy disruption, cue overload, cue biasing, or context biasing (Anderson and Bjork, 1994). A common theme among many of these non-inhibitory mechanisms is that retrieval strengthens the practiced items, which then has the effect of occluding, interfering with, or directing activation away from non-practiced items associated with the same retrieval cues (Anderson, 1983; McGeoch, 1942; Mensink and Raaijmakers, 1988; Raaijmakers and Shiffrin, 1981; Rundus, 1973).

Storm and Levy (2012) argued that proponents of the inhibitory account do not claim that non-inhibitory mechanisms cannot cause retrieval-induced forgetting. In fact, response competition from strong items and the resultant blocking of weaker items is precisely the situation that purportedly triggers the need for inhibition. It seems possible that both inhibition and interference contribute to some degree to all demonstrations of retrieval-induced forgetting. What inhibitory proponents have claimed is that many aspects of retrieval-induced forgetting are difficult to account for

by purely non-inhibitory processes. Thus, to provide evidence in support of inhibition, researchers have sought to demonstrate a pattern of forgetting that cannot be fully accounted for by non-inhibitory processes and that is consistent with the function that inhibition is presumed to afford.

Neuroimaging methods have also been employed to investigate the neural systems that are engaged when people attempt to resolve competition during retrieval. Functional magnetic resonance imaging studies have revealed that competitive retrieval practice engages the lateral and medial prefrontal cortices (PFCs; Kuhl, et al., 2007; Wimber, Rutschmann, Greenlee, and Bäuml, 2009), regions broadly considered to support cognitive control. Similarly, electroencephalogram studies have shown that retrieval practice is associated with enhanced positivity over frontal electrode sites (Johansson, et al., 2007). Kuhl, et al., (2007) expanded on these basic findings by showing that activity in both the lateral and medial PFC decreases across repeated retrieval-practice trials, as would be expected if each successive retrieval attempt required less cognitive control.

These findings are ambiguous, however, and fail to determine whether retrieval-induced forgetting is the result of interference or inhibition. PFC could be engaged in response to increased control demands due to the presence of competing

alternatives (i.e., blocking), or it could mediate an inhibitory process that is elicited by competition. In support of the inhibitory account, Kuhl, et al., found that decreases in the engagement of two distinct PFC regions—namely, the anterior cingulate cortex (ACC) and right anterior ventrolateral PFC—predicted how much retrieval-induced forgetting was observed on the final test.

More recent studies have revealed similar relationships between PFC activity and forgetting. Wimber, et al., (2009) found that increased recruitment of ACC and dorsolateral PFC during retrieval practice predicted subsequent retrieval-induced forgetting. Johansson, et al., (2007) found that their frontal event-related potential component predicted retrieval-induced forgetting. Hanslmayr, Staudigl, Aslan, and Bäuml (2010) found that increased theta power over right frontal sites during competitive retrieval predicted retrieval-induced forgetting. Finally, Wimber, et al., (2011) found that variation in genes regulating prefrontal dopamine predicted the magnitudes of both retrieval-induced forgetting and activation within right anterior PFC—including an anterior ventrolateral PFC region similar to the one identified by Kuhl, et al., (2007).

The cognitive neuroscience findings provide support for the fact that inaccessibility does not imply forgetting in a permanent sense, and when appropriate retrieval cues are provided, forgotten items can regain their accessibility (Storm and Levy 2012).

These observations suggest that forgetting is often a problem not so much of storage as of retrieval (Bjork and Bjork, 1992). The accessibility of an item will depend not only on its relations to the current set of cues, but on the relations between the current set of cues and other items in memory (Bjork and Bjork, 1992; Nairne, 2002, 2006). Thus, even if a target item is strongly associated to a given cue, if other items are more strongly associated to that cue, the target item will be difficult to retrieve.

Storm and Levy (2012) in a recent review suggested that inhibition may act during retrieval to suppress, or diminish the accessibility of, interfering items, in order to facilitate the retrieval of target items. Evidence supporting the role of inhibition in memory retrieval has come primarily from the empirical observation that retrieving a subset of items can cause the forgetting of other items. Researchers have long known about the negative consequences of retrieval (Brown, 1968; Roediger, 1974, 1978; Tulving and Arbuckle, 1963).

The finding has proven to be highly robust and general, emerging in many contexts and with a variety of materials; with factual propositions, (Macrae and MacLeod, 1999; Anderson and Bell, 2001; Gómez-Ariza, Lechuga, Pelegrina, and Bajo, 2005; phonological categories, Bajo, Gómez-Ariza, Fernandez, and Marful, 2006); text passages, (Carroll, Campbell-Ratcliffe, Murnane,

andPerfect, 2007; Chan, McDermott, and Roediger, 2006; Little, Storm, and Bjork, 2011); visuospatial materials, (Ciranniand and Shimamura, 1999); language selection, (Levy, McVeigh, Marful, and Anderson, 2007); arithmetic facts, (Phenix and Campbell, 2004); eyewitness memory, (Garcia-Bajos, Migueles, and Anderson, 2009; M. D. MacLeod, 2002; Saunders and MacLeod, 2002; Shaw, Bjork, and Handal, 1995); mental imagery, (Saunders, Fernandes, and Kosnes, 2009); creative problem solving, (Storm, Angello, and Bjork, 2011); autobiographical memory, (Barnier, Hung, and Conway, M.A. 2004; Storm and Jobe, 2012); and social contexts, (Dunn and Spellman, 2003; Storm, Bjork, and Bjork, 2005).

Barnier, Hung, and Conway, M.A. (2004) and Wessel and Hauer (2006) asked participants to generate autobiographical memories of differing emotional valence, which were then used as the stimuli in a RIF procedure. These studies produced contrasting results, with Barnier, et al., (2004) reporting RIF for positive, negative and neutral autobiographical memories. Although they predicted more RIF for neutral and positive memories than for negative ones, there was no interaction between RIF and valence. Wessel and Hauer (2006) used positive and negative autobiographical memories as stimuli and observed a RIF effect only in the negative condition.

Clinical disorders such as depression and schizophrenia as previously discussed are associated with a number of abnormalities of memory and retrieval, which could potentially play a part in causing or sustaining these disorders. These retrieval

abnormalities include over-selective memory with a bias to retrieval of distressing events (Bower 1981, Rusting and Dehart 2000), over-generalised retrieval (Williams 1999), and excessive rumination (Nolen-Hoeksema 2000, 2006). It is possible that these retrieval abnormalities may be associated with deficits in cognitive inhibition. Since the mechanism underlying RIF is believed to depend on such an inhibitory process (Anderson 2003), there is a possibility that RIF and other related measures of cognitive inhibition may be involved in these memory abnormalities. The role apparently played by RIF in suppressing unwanted memories raises the possibility that the RIF mechanism could also play a part in suppressing distressing intrusive thoughts, which are a feature of depression and schizophrenia (Lang, et al., 1999).

This was further investigated by Groome and Sterkaj (2010) for individuals with clinical depression; their findings revealed that the RIF effect was greatly reduced in the clinical sample in comparison to healthy controls. Demonstrating that mood may be an important mediating factor in the RIF paradigm, in line with Moulds and Kandris (2006), who investigated RIF for neutral and depression-related words in high- and low-dysphoric participants. Their hypothesis was that dysphoric individuals would have problems with inhibiting negative memories, and would therefore show a lack of RIF for depression-related words. Their findings confirmed this hypothesis, as RIF was observed for neutral words but not for the depressive stimuli. Interestingly this pattern was observed also for the low-dysphoric group. Studies suggest that

positive memories have many of the same properties as negative memories, e.g., in terms of intrusiveness (Berntsen, 1996, 2001). However it is questionable as to whether such lack of inhibition could be demonstrated for pleasurable memories as well.

Amir, Brigidi, Coles, and Foa (2001) investigated RIF for both positive and negative stimuli. They studied a group of individuals with generalised social phobia, where memories of negative aspects of social interactions can be intrusive and highly disturbing. Their stimuli consisted of negative social words (e.g., Dating–rejection), positive social words (Party–friends) and neutral non-social words (Fish–herring). Non-anxious controls demonstrated RIF for all categories, whereas the social phobics produced RIF only for the neutral and the positive words, and not for the psychopathology-relevant words. The findings were accounted for by the negative social words' intrusiveness for the individuals suffering from social phobia, making them resistant to the inhibition in RIF.

Amir, et al., reported that non-anxious controls showed RIF for both positive and negative words, but note that, as indicated by the category titles (conversation, party, job, dating) and the words (e.g., Conversation: argue, babble, criticism, nowhere, silence, sustain), there is no reason to believe that the negative words in this study were especially negative for the control group, so that the RIF might be interpreted

as the standard effect found for neutral words. The study by Moulds and Kandris (2006) suggests that no RIF effect would occur for negative words, as was the case in their low-dysphoria group.

Initially, it was argued that RIF would not occur on recognition memory tests, based on the idea that presentation of the item itself would release it from its inhibited state (Anderson, et al., 1994). However, Hicks and Starns (2004), and Veling and van Knippenberg (2004) have demonstrated the typical RIF effect on a cue-independent recognition test consisting of an old/new decision task. In the test phase the exemplars are presented one at a time without the category cue, implying that every non-practised exemplar of the category is actively suppressed on its own, and not only in the context of the common denominator: the category name. Furthermore, as noted by Perfect, Moulin, Conway, M.A. and Perry (2002), a reaction-timed cue-independent recognition test might be a more optimal measurement of the activation of a memory representation than recall, and, indeed, Veling and van Knippenberg (2004) found the typical RIF effect with response times as the dependent variable.

Using a response-timed recognition test is useful in other ways too. First, it is one way to eliminate an interpretation of RIF in terms of output interference: When recall is used as the final test, Rp+ items tend to be recalled first and thus may interfere with the recall of Rp− items, obviating the need for an explanation of any advantage

of Nrp over Rp− in terms of inhibition. Second, using a response-timed recognition test will reduce the possibility of floor effects, as may have been the case for the negative conditions in Moulds and Kandris' (2006) study.

An advantage of using a recognition test is that it allows one to shed light on the question of whether RIF is observed only for Rp− items or for all items from a studied category, including items not studied in the first phase of the experiment. This is important in terms of specifying the episodic or semantic nature of RIF. If the phenomenon is explained in terms of inhibition due to overlap of semantic features between Rp+ and Rp−, then retrieval practice should in fact inhibit the mental representations of all non-Rp+ category members, whether they were studied in the first phase of the experiment (as is the case for Rp− words) or not. In fact, this issue was first investigated by Perfect, et al., (2002) who, in the category verification task used in the test phase of their Experiment 5, included words not presented in the study phase but which were exemplars of studied categories.

The observation that there was no difference in response times between the extra-list items that came from Rp and Nrp categories led to the conclusion that RIF is only observed for words studied in an experiment's first phase and does not extend to other words from the same semantic category. Recently, Camp, Pecher, and Schmidt (2007) strongly supported this notion in a series of RIF experiments where

the participants performed a cue-independent recall test for words semantically related to the ones studied in the retrieval phase. The semantically-related words were not inhibited. Their results are more compatible with an account of RIF in terms of Racsmány and Conway's, M.A. (2006) concept of episodic inhibition, which has been applied to both deliberate and automatic forgetting.

According to episodic inhibition theory, episodic memory traces can have a pattern of activation and inhibition superimposed upon them, at the level of individual items within the trace, and independent of the strength of the episodic trace itself. The pattern has a priming effect that can increase or decrease the accessibility of the representations of individual items contained in the trace, over long periods. On this account, the retrieval practice of the Rp+ items leads to the pattern being activated for them and inhibited for the Rp− items. Thus RIF should not be observed for category members not seen in the experiment, but only for studied items that were not presented in the retrieval practice phase, i.e., Rp− items. The episodic inhibition account assumes that the inhibition will only emerge on a task requiring access to the episodic trace.

The evidence summarised above suggests that inhibition underlies retrieval-induced forgetting. This leads to the interesting conclusion that individuals with inhibitory deficits should demonstrate less retrieval-induced forgetting than populations without such deficits. This area however has not been extensively researched and the current findings are contradictory. Populations presumed to have inhibitory deficits

have been reported to have normal RIF (e.g., individuals with frontal-lobe damage, Conway, M.A. and Fthenaki, 2003; healthy older adults, Aslan, et al., 2007; Gómez-Ariza, Pelegrina, Lechuga, Suárez, and Bajo, 2009; young children, Ford, Keating, and Patel, 2004; Zellner and Bäuml, 2005; individuals with Alzheimer's disease, Moulin, et al., 2002; and individuals with schizophrenia, Nestor, et al., 2005).

However, there are several reasons why populations with assumed inhibitory deficits might exhibit normal levels of retrieval-induced forgetting. First, many of these studies did not independently verify inhibitory functioning. In the case of older adults, for example, perhaps a subset of individuals do not have any difficulties with inhibition, and it may be that it is these high-functioning individuals who are more likely to participate in experiments. Second, inhibition is unlikely to be an all-or-none resource. In fact, in their recent work, Ortega, Gómez-Ariza, Román, and Bajo (2012) found that healthy older adults exhibit normal levels of retrieval-induced forgetting when retrieval practice is undertaken under typical conditions, but significantly less retrieval-induced forgetting when retrieval practice is undertaken concurrently with a task that taxes executive control. This finding suggests that the consequences of inhibitory deficits for retrieval-induced forgetting may only become apparent when they are great enough to impede the successful inhibition of competing responses. When retrieval practice is made relatively simple, as is often

the case in research with clinical populations, individuals with subtle inhibitory deficits may be able to successfully suppress interfering items.

Perhaps the most important factor accounting for why populations with inhibitory deficits might exhibit normal levels of retrieval-induced forgetting concerns the correlated costs and benefits of inhibition (Anderson and Levy, 2007). Ironically, many of the aforementioned populations may have exhibited retrieval-induced forgetting specifically because of their inhibitory deficit. The idea is that retrieval-induced forgetting can be produced not only by inhibition during retrieval practice, but by the lack of inhibition at test. Because practiced items are strengthened, they are likely to interfere with the later recall of non practiced items from the same category. Thus, without the ability to inhibit the items strengthened during retrieval practice, participants with inhibitory deficits may be less able to overcome interference from those items and, as a consequence, may be less able to successfully retrieve non practiced items at test.

In their recent review Strom and Levy (2012) argue that the correlated-costs-and-benefits issue is most problematic in studies that fail to control for output interference, such as those that employ a category-cued final test. They also argue that the vast majority of studies that have shown normal levels of retrieval-induced forgetting in populations with presumed inhibitory deficits have employed just this

type of test (e.g., Conway, M.A. and Fthenaki, 2003; Ford, et al., 2004; Moulin, et al., 2002; Nestor,et al., 2005; Zellner and Bäuml, 2005). Storm and Levy (2012) argued that when output interference is controlled, populations with presumed inhibitory deficits generally do demonstrate impaired levels of retrieval-induced forgetting (e.g., schizophrenia patients, Soriano, et al., 2009; ADHD patients, Storm and White, 2010; and young children, Aslan and Bäuml, 2010).

Storm and White, for example, found that individuals diagnosed with ADHD exhibited normal levels of retrieval-induced forgetting on a category-cued final test but failed to exhibit any retrieval-induced forgetting on a category-plus-letter-stem-cued final test. However Groome and Sterkaj (2010) employed a category-cued final test in a clinically depressed population and did in fact demonstrate impaired RIF. Therefore suggesting that perhaps test type may not be the key underlying factor behind RIF. Anderson and Levy (2007) argued that the best way to control for the correlated-costs-and-benefits problem is to use a cue-independent final test, but the data reviewed above suggest that using an item-specific final test (category plus stem) may be sufficient.

1.7 Memory deficits in depression and schizophrenia

Difficulty inhibiting irrelevant information may play a central role in the aetiology of many clinical disorders. Three mechanisms have been implicated in the relationship

between biased cognitive processing and the dysregulation of emotion in depression: inhibitory processes and deficits in working memory, ruminative responses to negative mood states and negative life events, and the inability to use positive and rewarding stimuli to regulate negative mood (Joormann, Cooney, Atlas, Gotlib 2010).

A large number of studies have demonstrated that individuals with psychotic disorders such as schizophrenia or depressive psychosis demonstrate performance deficits on a wide range of WM tasks (Gold, Carpenter, Randolph, Goldberg, and Weinberger, 1997; Goldman-Rakic, 1994; Barch, et al., 1998, 2003; Cohen, et al., 1999; Gold, et al., 1997, Goldberg, et al., 1998, Gooding and Tallent 2001; Park and Holzman 1992; Park and Holzman 1993; Stone, et al., 1998 and Wexler, et al., 1998; Lee and Park 2005; Fuller, Luck, Braun, Robinson, McMahon and Gold 2009). Similarly individuals with other psychiatric disorders, such as unipolar major depression, also display WM deficits (Landro, et al., 2001; Merriam, et al., 1999; Pelosi et al 2000 and Sweeney, et al 1998., These abnormalities have been associated with activation of prefrontal cortex in both depression (Merriam, et al., 1999; Purcell, et al., 1997 and Sweeney, et al., 1998) and schizophrenia (Andreasen, et al., 1992; Perlstein, et al., 2001; Maller, et al., 2010; Cuervo-Lombard, et al., 2012 and Cano-Colino and Compete 2012).

There is growing evidence linking depression and schizophrenia with frontal lobe dysfunction for instance, imaging studies of depressed patients using positron emission tomography (PET) and regional cerebral blood flow (rCBF) have shown changes in areas including the left anterior cingulate and the left dorsolateral prefrontal cortex (Bench, et al., 1992;Maller, et al., 2010; Cuervo-Lombard., et al., 2012; Cano-Colino and Compete 2012) Furthermore, these changes have been related to cognitive and clinical dimensions (Dolan, et al., 1992). The role of the frontal lobes in human cognition is complex, but it is now well established that the prefrontal lobes are generally involved in the executive cognitive functions associated with disorders such as depression and psychosis.

Negative automatic thoughts and persistent rumination about negative events and negative mood states are hallmark features of depressive episodes. Cognitive models postulate that, by facilitating these negative thoughts, mood-congruent selective attention plays a central role in the aetiology, maintenance, and recurrence of depression (Beck, 1976 and Teasdale, 1988). Research indicates that selective attention involves at least two separate mechanisms: (a) orientation toward relevant stimuli; and (b) active disengagement from irrelevant stimuli through inhibition (Posner, 1995 and Milliken and Tipper, 1998). In this context, investigators have suggested that depressed individuals are not biased in their initial orientation toward negative stimuli, but instead, have difficulty disengaging their attention from this material (Joormann, 2004 and Joormann, et al., 2007).

To examine the formulation that inhibitory deficits underlie attentional biases observed in depression, negative affective priming (NAP) tasks have been used (Joormann, 2005 and Goeleven, et al., 2006). In negative priming studies, participants typically take longer to respond to a stimulus that they were previously instructed to ignore, or to a semantically related stimulus. This increased response latency is referred to as the negative priming effect, and is postulated to be caused by active inhibitory processes that keep previously irrelevant stimuli from entering working memory (Milliken and Tipper, 1998 and Tipper, 2001). In the NAP task, the negative priming effect is observed when ignoring an emotional stimulus results in a delayed response to a stimulus of the same valence that is presented as a target in a subsequent trial. This task, therefore, assesses individual differences in the inhibition of irrelevant emotional material.

Investigators have demonstrated that individuals diagnosed with current or past major depressive disorder (MDD), as well as dysphoric individuals, exhibited diminished negative priming (reflecting reduced inhibition) for negative words, compared to participants who had never been depressed (Joormann, 2004 and Goeleven, et al., 2006). Reduced inhibition has also been found to be associated with the tendency to ruminate in response to negative events (Joormann, 2006), suggesting that inhibitory deficits underlie the rumination associated with depression. These studies suggest that inhibitory deficits play an important role in the onset and maintenance of depression.

Similarly in psychosis, critical deficits in cognitive functions appear to reflect altered neural processing in the prefrontal cortex (PFC).Schizophrenia typically becomes manifest clinically during late adolescence or early adulthood. Disturbances in cognition, such as deficits in memory, attention, and executive function, appear to be core features of the illness because they may be present before the onset of psychosis, are persistent during the course of the illness, and appear to be the best predictor of long-term outcome. Some of these cognitive disturbances appear to be linked to dysfunction of working memory and the dorsolateral prefrontal cortex (PFC).

One of the primary symptoms of schizophrenia is auditory hallucinations (AH), similarities between AH and unwanted intrusive thoughts have increasingly been noted and several theories implicate the involvement of intrusive cognition in AH (Nayani and David, 1996, Morrison, 2001). Intrusive thoughts have been linked to a deficit in inhibition in other disorders such as Obsessive-Compulsive Disorder (Enright and Beech, 1993) and Post-Traumatic Stress Disorder (Vasterling, et al., 1998). There is considerable experimental evidence that schizophrenia is linked to a deficit in inhibition (Beech, et al., 1989, Brebion, et al., 1996) and Frith (1979) also suggested an association between AH and inhibition. However, a few studies that have investigated the role of inhibitory processes in AH have failed to demonstrate such a role using negative priming (Peters, et al., 2000) and interference (Brebion, et al., 1998) tasks. One of the reasons why these studies may have failed to find a

deficit in inhibition in AH may be because of the type of inhibitory processes measured by those tasks.

A conceptual distinction has been made between automatic and intentional forms of inhibition (Kipp, Harnishfeger, 1995). Negative priming and interference control are not categorised as intentional forms of inhibition, so the failure of previous studies to establish a relationship between AH and inhibition may be because it is a deficit in intentional inhibition that is critical to AH. Since AH are consciously experienced mental events, it is reasonable to argue that they may reflect impairment in intentional inhibition processes. In view of their importance for behaviour, processes that are involved in the creation and use of memory, such as encoding, maintenance and retrieval have been extensively researched.

However, one memory phenomenon that continues to be contentious is the question of whether we can inhibit the retrieval of specific memories (Baddeley 2012). While the last century has brought about a significant increase in our understanding of how memory information becomes less accessible, exemplified in numerous theoretical accounts of how forgetting occurs, it has focused mainly on processes that are automatic (for example interference and decay). Cognitive psychology and neuroscience has only recently probed into whether controlled aspects of memory

apply to the inhibition of retrieval. Consequently, there is little consensus on the specific mechanisms by which control may be exerted to inhibit memory retrieval.

A discussion of Storm and Levy's review in the previous section suggested that future research needs to investigate each population using tests that control for output order before a conclusion can be drawn on whether they suffer impaired levels of inhibitory-based retrieval-induced forgetting. This research aims to address this by directly comparing category cued and recognition RIF methodologies in a healthy population whilst controlling for critical mediating factors such as mood, smoking status and schizotypy. These are fundamental issues that have largely been ignored in RIF literature despite findings that such factors play a significant role in RIF (Edginton and Rusted 2003, Bäuml, Hung and Conway, M.A. 2004, Bäuml and Kuhbandner, 2007;Groome and Sterkaj 2010,). Controversies with RIF findings in populations with inhibitory deficits such as schizophrenia and depression indicate a need for further investigation. Based on the current evidence and the accounts of inhibitory theories these populations should demonstrate less retrieval-induced forgetting than populations without such deficits (Storm and Levy 2012) however, the mixed findings in the literature may reflect the neglect of these salient factors that have a direct impact on interpretation of reported data.

1.8 Main Aims

Based on the current literature it is clear that the study of cognitive aspects of depression and schizophrenia must be broadened by investigating neural and genetic factors that are related to cognitive dysfunction in these disorders. Such integrative investigations should aid to provide a more comprehensive understanding of how cognitive and biological factors interact to affect the onset, maintenance, and course of both depression and schizophrenia. The main objective of this thesis is to investigate the retrieval induced forgetting effect in clinical depression and psychotic disorders such as schizophrenia in comparison to healthy controls. It is aimed to incorporate a range of neuropsychological measures, to provide an indication of overall cognitive functioning of participants and to explore associations of these measures with the RIF effect.

A range of research strategies including, self-report questionnaires, neuropsychological assessment and the Retrieval Induced Forgetting paradigm are used to address these issues. The thesis describes those methodologies through a series of studies and presents the findings of the investigation with the aim of developing a greater understanding of inhibitory processes in schizophrenia and depression. Each study was treated as an independent inquiry containing specific aims and hypotheses, outlined within a designated chapter. The objectives and

predictions for those independent inquiries are detailed within the respective chapter that also include a review of the research literature relevant to those topics.

1.9 Main hypotheses

Based on the evidence summarised in this chapter the following hypotheses have are made:

I) Testing procedure will have an impact on the effect of Retrieval Induced Forgetting, such that the RIF effect observed using the category testing procedure will significantly vary from the RIF effect observed using the recognition testing procedure.

II) The Retrieval Induced Forgetting effect will be impaired among the depression and schizophrenia samples in comparison to that of the healthy controls.

III) Retrieval Induced Forgetting may be a heritable trait considering that brain structures have been implicated with the mechanism. Thus twin pairs may show no significant differences in the RIF effect. It is also predicted that twins with psychotic disorders will differentiate in their RIF effect in comparison to healthy twins.

IV) Retrieval Induced Forgetting will be mediated by factors such as mood and cigarette smoking, in that smoking will enhance the RIF effect and low mood will impair the RIF effect, in both clinical samples and healthy controls.

Chapter 2

General Methods and Recruitment

2.1 Introduction

This thesis consists of a series of self-contained investigations. A precise description of the research design, sample characteristics and methodology employed for each of those analyses appears in the relevant chapters. Each investigation is based on a different sample of participants; the general methodological approach however is consistent throughout the study and a common pattern of analysis is employed. In this section the studies' principle methodological procedures are outlined, providing an overview of the participant samples and recruitment strategies. Also a description of each test that has been used is provided with particular focus on the RIF paradigm as the central focus of this thesis.

2.2 Research design: general strategy

This study used a correlational design to investigate Retrieval Induced Forgetting in a sample of individuals with clinical depression, a sample of individuals with psychosis, a group of matched twins with and without psychosis and a group of healthy controls. Various statistical analyses were conducted including; bivariate correlations, analyses of variance (ANOVA) and independent samples t-tests. These analyses were selected to establish any associations between Retrieval Induced Forgetting and either depression or psychosis and also to establish any association

between RIF and any of the cognitive measures employed. Variables identified as potentially important predictors of the RIF effect in these exploratory analyses were then subjected to a series of multiple linear regression analyses to estimate the extent to which they could explain variations in the RIF effect.

2.3 Participants

Each individual chapter will provide specific details for the relevant samples under investigation. The overall participant sample comprised individuals diagnosed with either depression or schizophrenia and a group of healthy controls matched to the patients on the factors of age, gender, and years of education. Healthy control participants were recruited from the local community and the patient groups were recruited from one of two centres; the Institute of Psychiatry, King's College London and the local mental health organisation MIND, an independent registered charity that offers a range of services and mental health information for anyone living in the local area.

The clinical status of all participants was stable with a single psychiatric diagnosis, established for a number of years. Participants were all on prescribed antidepressant or antipsychotic medication. Ethical approval for the participation of the patient groups in the study was obtained from the MIND committee board and the NHS Central Office for Research Ethics (COREC) and the University of Westminster Research Ethics Committee.

Healthy participants were recruited through different local organisations e.g. sports and parenting clubs. The healthy controls were screened for depression with the BDII-II and were asked to report any history of mental illness including psychotic disorders.

Exclusion criteria for all participants were: English not spoken as a first language; aged under 18 or over 65; evidence of learning disabilities (as measure by IQ scores less than 75). In addition a history of any psychiatric illness was an exclusion criteria for the control participants.

The requirement for English as a first language was made due to the nature of the RIF task. The RIF stimuli were typical English word pairs that a non-native English speaker may not have encountered before i.e. names of birds. Finally, only participants whom successfully completed all stages of the research were included. Two people from the clinical sample and one person from the healthy control group were excluded from the analysis due to non-completion.

Collapsing Clinical and healthy Control Groups

Following separate analysis for each group the participants were collapsed into one whole group in chapters, 4, 5, and 6. The reason for this was to increase the statistical power, in establishing whether there was any association of the RIF effect with other neuropsychological measures. While it is acknowledge that this method has obvious limitations, as clinical samples cannot be assumed to be the same sample as healthy controls. This was purely exploratory sampling as mood,

schizotypy nor smoking status along with other neuropsychological measures have not previously been investigated in association with RIF. Therefore collapsing the data provided an opportunity to determine whether RIF was associated with these measures when statistical power was increased.

Combining all healthy controls

Following the findings from the clinical populations, it was considered important to conduct a separate analysis on the healthy controls alone. The purpose of this investigation was to further strengthen the finding that RIF was associated with smoking, mood and schizotypy, as there is previous evidence that RIF is mediated by smoking. The rational of investigating these measures on solely healthy controls was to establish any association of these measures with the RIF effect on a larger sample of participants, increasing the validity of findings.

2.4 Materials

2.4.1 RIF measurement

The RIF procedure used in the present study was a modified task, based on that established by Anderson, et al., (1994). The memory items for the RIF test consisted of 36 category-exemplar word pairs (e.g. Fruit-Apple) made up of six exemplars from each of six categories (See appendix I for a list of all words used in the paradigm) Items were selected from the frequency norms published by Van Overschelde,

Rawson, and Dunlosky (2004), in order to ensure that exemplars in each category were approximately equal to one another in respect of their frequency of use.

In a typical RIF paradigm as employed here (See next page), participants study a list of category–exemplar pairs (e.g. Fruit–orange). Participants are then cued to recall half of the exemplars from half of the presented categories by means of a category plus word stem cue (e.g. Fruit - or). The percentage of correctly recalled items for this phase is important in order to be able to establish that the mechanism which derives RIF was successfully completed, thus ensuring retrieval. The consequence of this retrieval practice phase is that three subsets of item are created; practiced items (Rp+ items), items that belong to the practiced category, but are not practiced (Rp- items), and items which were not practiced and belong to an unpracticed category (Nrp items). A retention interval of 15 to 20 minutes is allowed during which relevant questionnaire acted as distracters. Finally the final phase of the paradigm is conducted whereby the participants are presented with all of the studied category names and they are asked to recall as many exemplars as possible from each of the presented categories. Typically the recall of the practised exemplars (Rp +) is better than the baseline exemplars (Nrp) reflecting a measure of facilitation. Notably it is the impaired recall of the non-practised competitors (Rp −) relative to the baseline exemplars (Nrp) that is the key finding, which has become known as “retrieval-induced forgetting” a measure of inhibition and or interference.

2.4.2 Beck Depression Inventory II (BDI-II)

The participants also completed the Beck Depression Inventory II (Beck, Steer, and Brown, 1996) in order to measure the subjective level of depression at the time of testing. The BDI-II is an established measure of reported depression, with an internal consistency of 0.92.BDI-II is the world's most widely used instrument detecting clinical depression and it is in line with current depression criteria of the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV). The *BDI-II* consists of 21 items, which assess psychological and somatic aspects of depression in clinical patients and healthy controls. This instrument is not used in isolation for diagnostic purposes and a careful interpretation is required for anyone scoring above the 12 cut-off point. Each item contains a list of four statements arranged in increasing severity about a particular symptom of depression. This questionnaire was administered during the distracter task of the RIF paradigm and also served as a filler task to prevent rehearsal of the test items.

2.4.3 Brief Schizotypal Personality Questionnaire (SPQ-B)

The SPQ-B (Raine and Benishay, 1995), is a 22 item instrument which is based on the original and longer version SPQ. It is used to screen for schizotypal traits. Schizotypy describes a personality dimension seen in both mentally healthy people and in people experiencing psychotic disorders such as schizophrenia. It is an aspect of personality associated with paranoid thoughts, beliefs about the paranormal, and a general confusion in everyday thinking. In addition to the

experience of psychotic-like symptoms, people with schizotypal traits also share other similarities with people diagnosed with schizophrenia. These include: genetic abnormalities (Siever and Davis, 2004), structural brain abnormalities (Buchsbaum, et al., 1997; Dickey, et al., 1999; Silverman, et al., 1998) and neuropsychological deficits (Siever, et al, 2002).

The SPQ-B consists of the most reliable items from the original SPQ. The nine subscales are equally represented in this instrument in order to obtain sampling validity. The SPQ-B yields a total score, together with scores for each of the three main sub-factors (cognitive-perceptual, interpersonal, and disorganized). Item analysis of the SPQ-B produces essentially the same three-factor structure as is obtained from sub-scale analysis of the SPQ (Axelrod, et al., 2001), the SPQ-B factors correlate very highly with the SPQ factors. Internal reliabilities of these sub-scales range from .72 to .80 with a mean of .76. Axelrod, et al., (2001) obtained similar findings, with reliabilities ranging from .74 to .76. This questionnaire was administered during the retention interval (phase 3) of the RIF experiment, and thus like the BDI served also as a filler task to prevent rehearsal of the test items. This task was included in order to provide a measure of schizotypy at the time of testing and to establish any connection between the scores on this task and the retrieval induced forgetting effect. Individuals with schizophrenia are reported to have reduced RIF scores, therefore obtaining SPQ-B ratings would provide an indication

of whether reduced RIF scores would also be associated with schizotypal traits amongst the healthy control participants.

2.4.4 Hopkins Verbal Learning Test – HVLT

The HVLT (Brandt, 1991) offers a neuropsychological screening measure of immediate and delayed verbal memory (recognition and recall) for individuals 16 years and older. The HVLT consists of three learning trials, a delayed recall trial (20-25 minute delay), and a yes/no delayed recognition trial. This latter trial consisted of a randomised list that included the 12 target words and 12 non-target words, six of which were drawn from the same semantic categories as the targets. Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index. The HVLT-R has high test-retest reliability, and its construct, concurrent, and discriminant validity have been well established. The HVLT-R was administered by reading the words aloud, requiring the participant to verbally recall the list of words (immediately in the three learning trials and after a 20 – 30 minute delay). In the final recognition trial the participant is asked to identify presented words from a list of target and distracter words. This measure was included to enable exploration of any potential verbal learning deficits and the RIF effect, as discussed in the literature associations have been established between overall cognitive functioning and inhibitory deficits. Thus including a measure of verbal learning provided an indication of verbal learning capacity and enabled an exploration of its association to the RIF effect.

2.4.5 Mindful Attention Awareness Scale (MAAS)

The MAAS (Brown and Ryan 2003) is a 15-item scale designed to assess a core characteristic of dispositional mindfulness, namely, open or receptive awareness of and attention to what is taking place in the present. The scale shows strong psychometric properties and has been validated with college, community, and cancer patient samples. Correlational, quasi-experimental, and laboratory studies have shown that the MAAS taps a unique quality of consciousness that is related to, and predictive of, a variety of self-regulation and well-being constructs. The measure takes 10 minutes or less to complete. This measure was included as there have been some preliminary studies suggesting that there is an association between MAAS and the RIF effect (discussed in the introductory chapter). Thus exploring this measure in association with the RIF effect would provide a useful indication of any association or impact that mindfulness may potentially have on the RIF effect.

2.4.6 Ruminative Response Scale (RRS)

The RRS (Nolen-Hoeksema 2000) constituted 22 items addressing how often participants engaged in responses to feeling sad or depressed. The RRS assessed self-focused responses that included items such as, ‘’why do I have problems that other people do not have?’’ It also assessed responses that were symptom-focused i.e. think about your feeling of fatigue and achiness’’ and responses that were focused on the consequences of having a depressed mood i.e. ‘’I will not be able to do my job if I do not snap out of this’’. This questionnaire used a Likert scale with

scores ranging from 1 (never) to 4 (always). The RRS is an extensively used tool in clinical settings and research and has been shown to have good internal consistency. (Just and Alloy, 1997; Kuehner and Weber, 1999, Nolen-Hoeksema, 2000 and Spasojevic and Alloy 2001).

This questionnaire was administered during phase 3 of the RIF experiment in combination with the BDI-II and SPQ and acted as a filler task. The main purpose of including this measure was to establish any effects between rumination and the RIF effect. Depression has been reported to be associated with higher levels of rumination (Nolen-Hoeksema and Morrow 1991) and there is evidence that individuals with depression demonstrate reduced RIF scores. Therefore it was considered important to incorporate this measure.

2.4.7 The Wechsler Abbreviated Scale Intelligence (WASI)

The WASI is a nationally standardized short and reliable measure of intelligence and yields the three traditional Verbal, Performance and Full Scale IQ scores. The WASI consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. The four-subtest form was administered in approximately 30 minutes and resulted in VIQ, PIQ, and FSIQ scores. The VIQ score, a measure of crystallized abilities was provided by two types of measures; the Vocabulary subtest for

measuring word knowledge, verbal concept formation, and fund of knowledge, and the Similarities subtest for measuring verbal reasoning and concept formation.

The PIQ score is provided by two different types of performance measures, the Matrix Reasoning for measuring visual information processing and abstract reasoning skills, and Block Design for measuring the ability to analyze and synthesize abstract visual stimuli, nonverbal concept formation, visual perception and organization, simultaneous processing, visual-motor coordination, learning, and the ability to separate figure and ground in visual stimuli. This test was administered on a separate occasion to reduce testing fatigue and its effect on performance. This measure was employed in order to control for levels of intellectual functioning.

2.5 Recruitment

The programme of research took place in the UK, with a process of ongoing Recruitment from September 2008 to July 2011. Recruitment was conducted by the author of this thesis. Participants were recruited individually, informed consent was obtained for all participants who were provided with a participant information sheet that outlined the project (see appendix II).Participants were reassured that their participation was voluntary and that the information they provided would remain confidential and anonymous. All testing took place in a private room, upon

completion of the experiment participants were debriefed and given contact details of the researcher.

2.5.1 Participants from MIND (participants with depression and psychosis)

The patient sample was recruited from a MIND organisation centre based in Havering. Initially, five different mental health organisations (East London) were approached for the purposes of patient recruitment. Two centres opted not to take part and there was a protracted administrative delay in gaining study approval from a further two centres. The Mind Centre however, promptly approved the study, allowing access for recruitment and testing such that recruitment from other centres was unnecessary.

Access to this centre was facilitated by the researcher working there as a volunteer for six months (January – June 2006) and then being employed on a part-time basis as the centre drop-in coordinator. This meant that the participants were familiar with the researcher and were willing to consider participating in the research. The Chief Executive, assisted the researcher in the application process to gain approval from COREC and from the Director of MIND. Approval to conduct the study was provided in January 2007 (see appendix III, for approval letter).The Chief executive granted approval following detailed explanations of the research plan, procedures, and recruitment strategies, copies of materials and questionnaires that were to be used.

Ethical approval for the study was also obtained from the University of Westminster Ethics Committee

The principal method of recruitment from MIND involved the researcher regularly attending four different drop-in centres and speaking to potential participants individually. The study was explained to each interested participant in detail and an information sheet (see appendix II) was provided for them to take away and consider whether they wished to participate. For each participant, a suitable appointment was arranged for the researcher to attend the centre and conduct the study. An additional recruitment approach involved displaying a poster at the centre along with suggested appointment times. As there were a number of tests involved in this study, IQ (WASI) testing was carried out on a separate day thus each participant was tested on two occasions. All testing took place individually in a quiet room within one of the four MIND centre premises. In agreement with all participants and the MIND centre manager, a donation was made to the MIND organisation, to thank the centre's staff and the participants for their support.

2.5.2 Participants from Institute of Psychiatry - Control and Twins with Psychotic Disorders

The research was employed as a research fellow in association with the Institute Of Psychiatry, the Maudsley hospital from September 2008 – September 2010, as part of an ongoing twins project. Twins with schizophrenia were recruited nationally

throughout the United Kingdom from National Health Service treatment centres through referrals by their treating psychiatrist. In the United Kingdom, the National Health Service is a comprehensive national treatment service funded centrally and free at the point of delivery for all aspects of health care. By virtue of its financial and organizational structure, it is completely inclusive and as a consequence cares for most patients with schizophrenia, making it a very representative system from which to recruit. Control twins were recruited from a volunteer twin register held at the Institute of Psychiatry, London, England.

Exclusion criteria applied to all of the groups were those of: an age younger than 18 years, a history of a neurological disorder or of a systemic illness with known neurological complications, a history of significant head injury associated with loss of consciousness for more than 1 minute and current harmful substance use or dependence (defined as within the last 12 months). No candidate included in the study had a psychotic illness directly attributable to the harmful use of illicit substances. The study was approved by the UK Multicentre Research Ethics Committee and all of the participants gave written informed consent before participating.

2.5.3 Recruitment of healthy control participants

The healthy control participants were recruited from an organisation based in Havering, constituting parents, grandparents and carers of a local under 10s football

team. The manager's verbal approval was obtained to approach the parents and e-mailed all the parents of the team a copy of the poster detailing the study (see appendix IV). As part of the recruitment process the researcher also approached parents directly after: matches, group meetings, or presentation gatherings and on some occasions personally contacted participants via phone or e-mail. Interested individuals were given information sheets outlining the study that also contained the researcher's contact details. The participants were given the option to either be entered into a prize draw to win an 'IPod touch' or to receive a high street gift voucher as a token of appreciation for their support on this study. The gift vouchers were distributed at the end of the second experimental procedure whereas the draw took place upon completion of all data collection (July 2011) during a club social event.

2.6 Ethical considerations

The research presented in this thesis was carried out according to the British Psychological Society's (BPS) Code of Conduct, Ethical Principles and Guidelines, with special reference to the Principles for Conducting Research with Human Participants section. The University of Westminster Code of Practice Governing the Ethical Conduct of Investigations, Demonstrations, Research and Experiments provided was also consulted. Ethical approval for the study was obtained from the University of Westminster Ethics Committee.

For all aspects of the research, ethical implications and psychological consequences of taking part were viewed from the standpoint of the participants. Every effort was made to engender mutual respect and confidence between the researcher and those taking part. All participation was voluntary and participation was only encouraged if participants felt comfortable to do so, as some of the questionnaires may have caused upsetting thoughts. Due to the nature of the research, any deception or withholding of information was unnecessary. Thus, volunteers were fully briefed regarding all aspects, including the procedure, aims and rationale for the study. All reasonable steps were taken to ensure that participants understood the nature of the investigation; both verbal and written information was provided.

All participants provided informed written consent. Upon giving consent, participants were given a copy of both the participant information sheet and the consent form to take away with them (see Appendices II). No participant had impairments in either communication or understanding which prevented them from being able to give their informed consent. No direct monetary incentive was offered, although participants were gifted with a high street voucher upon completion of the study and for the clinical sample a donation was made to the organisation to be used on the clients.

By consenting to take part, participants were not increasing the probability of exposure to risks or harm greater than or additional to those encountered in their

normal lifestyles. Participants were not subject to any physical discomfort although there was a minimal risk of emotional discomfort that could potentially have arisen from completing the questionnaires. Participants were assured that they did not have to disclose any information they did not wish to, that they could leave the investigation at any time and that any information given would be kept confidential and anonymous. In particular, this reassurance helped to create a safe testing context for the participant.

Neither the RIF procedure nor the questionnaires gave rise to any information which the researcher believed could endanger the participant's well-being. As per the organisational (MIND) policy participants were given the researcher's contact details to enable them to ask questions or express concern prior to or following participation. At any point, volunteers were not pressurised to take part in or remain in the investigation. Participants were informed of their right to withdraw from the research at any point, including the right to withdraw consent retrospectively and to require that their own data be destroyed.

Due to the initial full briefing, a formal debrief was deemed unnecessary. However after taking part, participants were given the opportunity to discuss with the investigator their experience of the research, which helped to monitor any unforeseen negative outcomes or misconceptions. Participants were encouraged to

give their feedback regarding how they felt about doing the study. They were also informed that they could contact the researcher via email at any time if they wished to be informed about the research findings. Participants were assured that all information obtained during the course of the research would be confidential, and that only aggregated data would be used in any subsequent publication. Volunteers were reassured that their information would be used strictly for the purposes of the present work.

Participants were also informed that all data would be destroyed in accordance with university policy. Steps were taken to preserve the confidentiality of information acquired through the research conducted in this thesis. Participants' names were coded separately rendering written and computerised records identifiable by only the researcher. Files of questionnaire data were stored in a locked room in the Regent Street campus of the University of Westminster. The researcher was custodian of the data and computerised data were only accessible by password, known only to the researcher. Anonymous computer data files were viewable only by the supervisory team, all of whom were aware of confidentiality issues, and no one other than the researcher held copies of the data files.

Chapter 3

Retrieval Induced Forgetting: A comparison between category-cued and recognition recall testing procedures

3.1 Introduction

This chapter will outline an investigation that examines two different retrieval induced forgetting procedures within a healthy population. The focus of this chapter is on exploring specific differences between the strength of the RIF effect produced by category cued and recognition recall procedures. These findings will also be explored for association with various cognitive measures and impact of mood and smoking. The introduction comprises three main sections: 1) Outline and differentiation of the two paradigms, 2) current explanations of the RIF phenomenon 3) a general review of the current literature employing the main RIF procedures. Following the introduction a study comparing category cued and recognition RIF procedures in a sample of one-hundred and twenty seven healthy controls is described.

3.2 Outline and differentiation of the two paradigms

Retrieval-induced forgetting (RIF) has been established as a robust phenomenon, which holds that repeated retrieval of specific information impairs retrieval of related or similar information whilst not affecting unrelated material (Anderson, Bjork and Bjork 1994). Retrieval-induced forgetting has been demonstrated in several ways. Anderson, et al., (1994) established a standard procedure for demonstrating RIF, which involves the presentation of a list of category exemplars divided into several distinct semantic categories, some of which are subsequently retrieved several times. Participants are then tested for their retrieval of the entire wordlist. It is found that not only are the practised words (Rp+) better retrieved than the unpractised words, but also that unpractised words from a practiced category (Rp-) are poorly retrieved in comparison with the unpractised words from an unpractised category (Nrp). Most commonly the RIF procedure follows three main phases, a study phase, a retrieval practice phase and a test phase following a twenty minute delay (see chapter one, for a detailed outline).

The main differentiations between the paradigms lie in the test phase and the way in which recall is prompted in the final phase. The standard procedure is the category cued recall whereby at the final test phase only the name of the category is presented and the participant is required to list as many items as possible for each category.RIF has been demonstrated in a wide range of tests, including word-stem

completion (Anderson, et al., 1994; Bäuml and Aslan, 2004), item recognition (Hicks and Starns, 2004; Spitzer and Bäuml, 2007), and tests using independent probes, i.e., novel retrieval cues not used until the test phase of the experiment (Anderson & Spellman, 1995; Saunders & MacLeod, 2006).

Other work has extended the effect to social traits (Macrae and MacLeod, 1999; MacLeod and Macrae, 2001), visuospatial materials (Ciranni and Shimamura, 1999), and visual scenes (Koutstaal, Schacter, Johnson, and Galluccio, 1999). Retrieval-induced forgetting has also been found using naturalistic eyewitness procedures (MacLeod, 2002; Shaw, Bjork, and Handel, 1995). For example, Shaw, et al., (1995) studied adults' memory for a simulated robbery using slides for two categories of items in the victim's apartment (books and clothing). Following a focused interrogation, participants demonstrated a greater recall of items that were from an unrelated (unpractised) category compared to novel items from a related category.

3.2.1 Current explanations of the RIF occurrence

As outlined in the general introductory section both inhibitory and interference processes have been identified as potential mechanisms that may underlie these automatic effects of retrieval. Interference processes have been identified as a

potential manifestation of strength-dependent competition within the semantic network. According to this theory, retrieval practice increases the retrieval strength of the rehearsed items such that they readily come to mind during the final memory test and block access to the unrehearsed items. This view receives support from observations of output interference and part-set cuing, even without retrieval practice for a subset of the studied items. Output interference refers to the fact that the probability of recalling a particular item declines at later stages in the testing sequence (Roediger and Schmidt, 1980). Similarly, when participants are given part of a previously studied category as a cue in the part-set cuing procedure, their ability to recall the remaining members is impaired relative to the situation where no cues are provided (Nickerson, 1984). Both effects can be attributed to strength-dependent competition if it is assumed that presenting studied items on the test increases their retrieval strength relative to un-presented items

Inhibitory accounts suggest that retrieval-induced forgetting is the consequence of a process that resolves competition and facilitates retrieval. A variety of evidence favours the view that competitors to the target items are actively suppressed during the retrieval practice through the operation of inhibitory processes designed to facilitate access to the rehearsed information. At least for relatively short retention intervals, this suppression of competitors generalises to the final memory test, even

though the need for suppression is now obsolete (Anderson, et al., 1994; Levy & Anderson, 2002).

There are several sources of support for an inhibitory account of retrieval-induced forgetting. First, the effect appears even when the test procedure is arranged to counteract strength-dependent interference by forcing participants to respond to the competitors before the practised examples, for example, by using category-plus-stem cued recall (Anderson, et al., 1994). Second, retrieval impairment is greater when competitors are of high rather than low taxonomic frequency for the category, suggesting that strong competitors require greater inhibition than weak competitors during the retrieval practice (Anderson, et al., 1994). Third, merely presenting a subset of items for additional study does not impair the subsequent retrieval of related items, despite producing substantial facilitation of recall for the instances that received the additional study presentations (Anderson, Bjork, and Bjork, 2000; Ciranni and Shimamura, 1999). Fourth, retrieval-induced forgetting is reduced when participants are instructed to integrate studied material during encoding.

This can be explained by assuming that initial integration of targets and competitors allows the facilitation accruing to the rehearsed information during retrieval practice to generalize to the competitors and overcome their inhibition (Anderson, Green, and McCulloch, 2000; Anderson and McCulloch, 1999). Indeed, a strong version of the

inhibitory account holds that retrieval-induced forgetting reflects not only impaired access to the non-practised items (i.e. retrieval inhibition) but, crucially, reduced availability of their memory traces (i.e. representational inhibition). In other words, retrieval practice is argued to produce real suppression of the activation levels for the competitors (see Moulin, Perfect, Conway, M.A and Perry, 2002, for a discussion of this issue).The strong inhibitory view receives support from evidence that impaired recall of competitors generalizes to different retrieval cues than those used during the practice sessions, a phenomenon known ascue-independent forgetting (Anderson & Spellman, 1995). There is also evidence that nicotine, a cholinergic agonist, may enhance inhibition on the RIF task (Edginton and Rusted 2003).

The extent to which RIF is a reliable phenomenon has not been investigated fully, as discussed above there have been different theories put forward to explain this occurrence. The interference theory proposes that the retrieval of one item simply increases the strength of association between that item and its cue, which reduces the chance of that cue generating a rival item (Camp, Pecher, and Schmidt, 2007; Moulin, Perfect, Conway, and Perry, 2002). In contrast the inhibition theory assumes that the retrieval of one item leads to a reduction in the actual memory strength of a rival item, which will apply to any retrieval cue (Anderson, 2003; Anderson and Levy, 2007; Anderson and Spellman, 1995; Levy and Anderson, 2008). Several studies have attempted to establish whether the RIF effect is restricted to the original cue or

whether it generalises to other, independent cues (i.e., where different cues are used for retrieval practice and final test). Some studies have reported the occurrence of RIF with independent cues (Anderson and Spellman, 1995; Aslan, Bauml, and Pastotter, 2007; Saunders and MacLeod, 2002, 2006) but other studies have not (Camp, et al., 2007; Perfect et al., 2002).

3.2.3 A general review of the current literature employing the various RIF procedures.

There appears to be reasonably strong support for the hypothesis that an inhibitory process acts during retrieval to resolve competition and that this process is a major, although not the sole, factor underlying retrieval-induced forgetting. Although some lines of evidence have been challenged (e.g., Camp, et al., 2009; Jakab and Raaijmakers, 2009; Perfect, et al., 2004), and some investigators are sceptical about inhibitory mechanisms in general (e.g., MacLeo,d et al., 2003), at present no clearly articulated alternative theories can account for all of the sources of the evidence. In this sense the current evidence, appears to lean more towards the idea that inhibition plays a role in memory than to assume that it does not. A crucial role of inhibitory mechanisms in the process of efficient remembering has been identified (Schacter 2001; Miyake et al. 2000; Friedman and Miyake 2004; Groome and Grant 2005). That is, the suppression of irrelevant information is key to the effective

processing of relevant material. Edginton and Rusted (2003) reported positive effects of nicotine on the ability to inhibit task-irrelevant semantic information.

Inhibition is an important process of memory that has been argued to facilitate recall in everyday events, and successful inhibition may be related to superior cognitive functioning. For instance Storm and Jobe (2012) found that individuals who exhibit greater levels of retrieval-induced forgetting recall significantly fewer negative events on an autobiographical memory task than individuals who exhibit reduced levels of retrieval-induced forgetting. Storm and Jobe (2012) argued that participants with greater inhibitory ability as evidenced by their retrieval-induced-forgetting scores are more likely to inhibit the recall of negative memories; despite the fact that such memories have the potential to serve as appropriate responses on the autobiographical memory task. In this case, a bias toward remembering positive information about one's self and maintaining positive affect may be the cause of negative information (see chapter four for further discussion) being targeted by inhibition, as opposed to such information being targeted because it is identified as non-target.

Further evidence for the function of inhibition in memory has emerged from studies of individuals with schizophrenia, who are known to exhibit inhibitory impairments in response suppression and selective attention (Soriano, et al., 2009; Laplante, Everett and Thomas, 2011). Normal RIF performance has been observed in individuals with schizophrenia when using letter cues in the final RIF recall test

(AhnAllen, Nestor, McCarley, and Shenton, 2007; Nestor, et al., 2005), but a recent study using recognition recall at the final RIF retrieval test has reported a significant reduction in the RIF effect compared with healthy controls (Soriano, Jimenez, Roman and Bajo, 2009). They also found that individuals with schizophrenia suffer from critical impairments in inhibitory processes involved in memory retrieval, similar to the inhibitory deficits found in other cognitive domains. Although evidence suggests that executive functions are separable and that different executive functions contribute differentially to various executive tasks (Miyake, et al., 2000).

Miyake, et al., (2000) investigated three main aspects of executive function; shifting between tasks or mental sets, updating and monitoring of working memory representations and inhibition of dominant or prepotent responses. The authors reported that these functions were distinguishable, although not completely independent. Miyake, et al., also suggested that unity amongst executive functions may be accounted for by inhibition, as all executive functions involve some inhibitory processes to function properly (e.g. ignoring previous incoming information in a working memory task and changing to a new mental set).

Research has demonstrated that executive functioning is a good predictor of performance, with some studies showing this result even after controlling for other potential explanatory factors such as long-term memory retrieval, phonological

processing, and speed of information processing. Indeed, Ozonoff and Jensen (1999) propose “executive profiles” for various developmental disorders. For example, children with autism typically show problems on executive tasks requiring flexibility and planning, but they perform normally on tasks involving inhibition. Children with ADHD show the opposite pattern of results, having difficulty on inhibition tasks, but not on tasks requiring flexibility (Bull and Scerif, 2001). Further support for the notion that inhibition may be a unifying function in executive processes also comes from the hybrid model of executive functions proposed by Barkley (1997). Barkley’s model proposes that behavioural inhibition permits the proficient performance of executive functions (e.g., working memory and self-regulation), which, in turn, influences the capacity to produce goal-directed behaviour in novel situations.

It has been proposed that variations in the strength of the RIF effect in individuals might be associated with a variety of other cognitive and clinical factors. Groome and Sterkaj (2010) found that the RIF effect was significantly reduced in individuals suffering from clinical depression, this finding was consistent with that of Bauml and Kuhbandner (2007) who reported that the RIF effect was significantly reduced in dysphoric members of the normal population (i.e., normal participants subjected to mood induction techniques). However, some interpretations of such correlation studies rely on the assumption that there are individual differences in RIF which are

stable over time. In other words, each individual has their own reasonably stable level of RIF, so that an individual producing a high RIF score on one occasion will show the same high RIF score on a future occasion.

Research has also focussed on other potential correlates of RIF including cognitive failures (Groome and Grant 2005). The authors reported a significant inverse correlation between RIF and the Cognitive Failures Questionnaire, meaning that individuals showing a weak RIF effect report more memory failures in everyday life. This finding offers support for the view that RIF may play a part in facilitating selective retrieval in real-life situations. However it must be acknowledged that the nature of the cognitive failures questionnaire is subjective and may not reflect inhibitory processes per se. The role apparently played by RIF in suppressing unwanted memories raises the possibility that the RIF mechanism could also play a part in suppressing distressing intrusive thoughts (Nolen-Hoeksema 2000, 2007), which are a feature of many psychiatric disorders and are thought to play a role in causing or aggravating those disorders (Lang, et al., 1999). It is however difficult to distinguish which aspects of inhibition are involved considering that there may be several inhibitory processes (Miyake, et al., 2000).

Neurocognitive studies have demonstrated that neural signals for inhibited items are reduced at test (Spitzer, Hanslmayr, Opitz, Mecklinger, andBäuml, 2009; Wimber, et

al., 2009) and inhibitory control is generally believed to be a frontally mediated, resource-demanding process (Conway, A.R.A and Engle, 1994; Kane and Engle, 2002). In line with this view, RIF has been reported to be diminished in individuals with low working memory capacity (WMC) (Aslan and Bäuml, 2011) and has been predicted by frontal activations during retrieval practice (Kuhl, Dudukovic, Kahn, and Wagner, 2007; Wimber, Rutschmann, Greenlee, and Bäuml, 2009). Indeed there has been evidence that smoking improves cognitive measures scores in individuals with schizophrenia (see chapter five for a further details).

One speculative explanation for why retrieval-induced forgetting persists is that, in addition to resolving interference during a current retrieval attempt, inhibition may prevent interference from occurring during future retrieval attempts. More specifically, if an item is inappropriately activated during one retrieval attempt, there might be an advantage to making that item less likely to be activated during a future retrieval attempt. In some instances, having the persistence of non-retrieval would be maladaptive, particularly if the competitors were to become relevant targets at a later time. More generally, however, the persisting consequences of inhibition might provide a mechanism for updating long-term memory in a way that meets the continuously changing needs of the environment (Anderson, 1989; Anderson & Schooler, 1991; Bjork and Bjork, 1988; Bjork, 1978), inhibition itself may not necessarily need to persist in order to have a persisting effect. By rendering competing items even temporarily less accessible, those items may be deprived of

the benefits of additional retrieval practice and be less likely to be integrated with the consolidation of new information. Indeed, the power of inhibition to update long-term memory may lie primarily in its ability to influence subsequent patterns of learning and rehearsal.

Another theoretical challenge will be to explain how and why the consequences of inhibition persist. As MacLeod and Macrae (2001, p. 149) argued, “Inhibitory effects need only endure until perceivers have satisfied their current processing objective. For this reason, it would be counterproductive if temporary forgetting endured for a considerable period of time. Indeed, if inhibition were to last indefinitely, its effects would be equivalent to the permanent erasure of items from memory.” Although the exact temporal boundary conditions of retrieval-induced forgetting have yet to be determined, the effect clearly does persist beyond the current processing objective, sometimes affecting recall as much as a week later (e.g., Garcia-Bajos, et al., 2009; Storm, Bjork, and Bjork, 2012; Chan, 2009; MacLeod and Macrae, 2001).

It seems possible that cue-dependent forgetting might make more functional sense than cue-independent forgetting. To adaptively update the future accessibility of an item in memory, that item should be rendered inaccessible in response to the particular cues and contexts that prompted its inappropriate activation, while allowing it to remain accessible given other cues and contexts. Consequently, although an item may interfere with retrieval and be inhibited in response to one cue, that same

item could retain its accessibility if targeted by another, more appropriate cue. Over time, the selective consequences of retrieval practice and inhibition might act together in such a way that information becomes more accessible in contexts in which it is likely to be useful, and less accessible in contexts in which it is less likely to be useful. However little attention has been given to the application of the different RIF procedures, using a standard category-cued recall procedure compared to recognition recall to determine their impact on the actual RIF effect.

A study investigating the RIF effect in children adopted both the category cued recall and the recognition recall procedures to explore differences in the RIF effect (Ford, Keating and Patel 2004). The findings revealed no significant difference between the RIF procedure employed and the RIF effect. In fact it is one of the few studies to document the existence of the RIF effect in children and young adults. Ford, et al., (2004) found that order of output of Rp+ and Rp-examples was not reliably associated with the magnitude of the effect. Likewise, in line with previous investigations that have controlled output order (Anderson, et al., 1994), the recognition-memory procedure used by Ford, et al., demonstrated significant retrieval impairment for Rp- examples, even when they were presented before the Rp+ examples. Indeed, sequence effects were in the opposite direction to that predicted by a strength-dependent interference account because prior presentation of the weak Rp- examples had a more damaging effect on retrieval of the

strengthened Rp+ examples than was the case for the reverse presentation order. This provides strong evidence that the RIF procedure employed may not be an important factor in determining the RIF effect as previously suggested (Anderson, 2003; Anderson and Levy, 2007; Anderson and Spellman, 1995; Levy and Anderson, 2008).

Studies using the category plus stem-cued recall procedure have similarly revealed decrements of recall accuracy for Rp+ examples following prior presentation of Rp- examples, although this trend has been analysed only in the wider context of output interference averaged across all item types (Anderson, et al., 1994, 2000; Anderson and McCulloch, 1999). Using a stem-cued recall paradigm that constrained participants' sequence of memory retrieval, Bauml (1998) demonstrated that output interference is better explained by retrieval suppression than by strength-dependent competition. Consistent with the finding of Anderson, et al., (1994) that retrieval-induced forgetting afflicts strong category members more than weak category members, Bauml (1997) observed that prior recall of weaker items reliably impaired the subsequent recall of stronger items, whereas prior recall of stronger items failed to impair, and instead facilitated, the subsequent recall of weaker items. Similarly Edginton and Rusted (2003) reported that nicotine enhanced inhibition for weaker items.

While findings of significant associations between RIF and other factors support the view that the RIF effect is a robust one, (the relative strength of which may be subject to individual differences in cognitive and psychological functioning), no study to date has provided specific evidence for such reliable differences in terms of test/retest reliability of RIF performance. Potts, et al., (2010) conducted a series of studies to test whether the pattern of variations in the RIF effect seen across individuals at one time point, would be observed in the same individuals when tested a second time. They employed, category cued procedure, category-plus-stem cued, recognition testing and repeated the tests with different items one week later. Their findings revealed that the RIF effect was not consistent when tested with the same procedure after a one week interval. In one experiment the category cued procedure was conducted using the same test items on two occasions and a significant correlation was found, however this could be attributed to remembering the items so this study was not able to determine whether the RIF effect is a consistent finding.

To date, there is little evidence for the reliability of the different RIF test measures currently available and there is significant dispute over which procedure or procedures produce an accurate measure of RIF. It is therefore necessary to investigate the different RIF procedures in order to determine whether there are significant differences between the experimental paradigms and whether the measures are consistent between tasks and over time.

Aims

The evidence summarised above suggests that there is need for further exploration into the consistency of RIF. The primary objective of the current study is to examine whether the RIF effect is a consistent measure when tested on different occasions and with different procedures. This study will also address whether the strength of the RIF effect will be significantly affected by different RIF testing procedures, namely the category cued and the recognition recall procedures. Finally this study will incorporate specific cognitive measures to test for any association between cognitive functioning and these RIF measures. As the evidence is unclear it is difficult to predict a direction of findings, however it is hypothesised that both procedures will reveal a significant RIF effect and that this effect will be associated with other measures of cognitive function notably verbal memory and executive function. It is also predicted that the RIF effect will significantly correlate with smoking status considering evidence suggest that nicotine enhances RIF.

Methods

Design

A repeated measures design was used whereby participants underwent testing for the RIF effect at two time points. (A three month delay between time points was implemented). At the first time point participants were tested using the category

cued procedure and on the second occasion the recognition procedure was used. (The order of test-type was counterbalanced for half the sample). There were three main stages to the analysis:

i) A repeated measures analysis of RIF type. This analysis was implemented to evaluate whether there were significant within-group differences in the RIF effect based on the type of RIF procedure employed.

ii) A correlational analysis to determine the extent to which RIF scores obtained on the category cued procedure are associated with those found on the recognition procedure.

iii) A within-group analysis designed to determine the strength of associations between RIF, mood and verbal learning.

Participants

Participants were 127 psychology undergraduate students, 105 females and 22 males with a mean age of 20 (SD= 3.7). The mean (± SD) level of education in years was 13. 4 (1.5), 45.7% were smokers and all spoke English as a first language with no participants reporting a history of mental illness. Participation was voluntary but participants were awarded course credits as part of a departmental research scheme.

Materials and Procedures

Two standard retrieval practice paradigms were used, category-cued recall and recognition which are outlined below. Both tests comprised four phases, a study phase, a retrieval practice phase, a distracter phase and a final test phase. The two versions of the RIF task were constructed according to the standard procedure devised by Anderson, et al., (1994). Tests were counter balanced, half of the participants received one variant of RIF i.e. category cued recall in the first experiment and recognition recall in the second experiment. A period of three months was considered to be a reasonable time to elapse in order to control for memorability of procedures prior to retesting. The following cognitive assessments were administered; the BDI-II, the SPQ-B, the RRS and the Mindfulness scale as outlined in the general methodology section.

The category-cued test consisted of 36 category-exemplar word pairs (fruit-apple), comprising six exemplars from each of six categories. Items were selected from a recently updated version (Van Overschelde, Rawson, and Dunlosky, 2004) of the traditional Battig and Montague (1969) category norms. The average taxonomic rank of exemplars in each set was equivalent, at 6.3, and categories within each set were equated for average taxonomic rank of items. Within each category, no two items began with the same letter. All participants underwent four main phases: study, retrieval practice, retention interval, and final retrieval test. Retrieval practice generated three types of items: practiced items (Rp+), unpracticed items from the

practiced categories (Rp-), and unpracticed items from the unpracticed categories (Nrp).

The RIF effect was measured by subtracting the difference between the Nrp- and Rp- scores, both expressed as percentage scores. Across participants, target items served as either Rp+, Rp-, or Nrp an equal number of times. This was done to control for variations in memorability of the test items. The item sets were made up into a specially designed computer programme (see appendix), which presented the items in order as per the standard RIF procedure and contained full instructions for each phase. To control for order effects there were four different presentation sequences (see appendix I, for outline of order items) that were counterbalanced. The computerised programme enabled typing of responses and stored the words in the retrieval practice phase and the final tests phase. The results were stored by the programme based on a unique participant number and ID.

The Recognition test consisted of48 test items, made up of 12 practiced items (Rp+), 12 un-practiced items from practiced categories (Rp_), and a further 24 un-practiced items from un-practiced categories (Nrp). The order of output in this experiment was controlled by the cues provided, the 24 Nrp items were divided into 12 Nrp- items presented in the first half of the retrieval list as controls for the Rp- items and 12 Nrp+ items presented in the second half as controls for the Rp+ items. The

materials used were drawn from Anderson, et al., (1994). Exemplars had an average taxonomic rank order of eight according to the Battig and Montague (1969) category norms. No two items in a category began with the same letter.

The learning and retrieval-practice phases were presented within a Microsoft PowerPoint presentation. The final test was presented as a paper and pen task and consisted of a list comprising the 48 test items interspersed with 48 distracter items. Output interference was controlled by presenting the Rp- and Nrp- items in the first half of the retrieval checklist, while the Rp+ and Nrp+ items were presented in the second half. The first half of the recognition list thus contained the 12 Rp- items and the 12 Nrp- items, together with 24 distracter items, all mixed together in a random order. The second half of the recognition list contained the 12 Rp+ items and the 12 Nrp+ items, and a further 24 distracter items, again presented in a random order. Participants were required to indicate whether or not they recognised each of the 96 items from the initial studied list by circling ‘‘yes’’ or ‘‘no’’ against each word on the list. Distracter items were words chosen from the same eight categories as the 48test items presented previously, and they were again selected from category norm tables (Van Overschelde, et al., 2004) to ensure comparable frequencies across the lists. The design of this recognition test was based on the procedure used by Soriano, et al., (2009).

The procedure used for the recognition test was similar to that used for the category cued procedure except for the use of a recognition procedure as the final retrieval test. The final test was administered as a paper and pen task. No time limit was imposed on completion of the final test but participants were instructed to work through the items as quickly as possible and not to return to a previous item.

Results

Category cued - Retrieval Induced Forgetting Effect

Table 1.1shows the percentages of correct recall and standard deviations in the final recall test for each RIF version and practice condition. The percentage of correct recall in the retrieval practice phase was 94.9for the recognition test version and 94.7 for the category cued test; this difference was not significant between the two test types (t = -.197, p = .923). A significant effect of RIF was found for both the category cued test procedure ($F_{(1:126)}$ = 135.281,MSE = 176.945 p < .0005, partial η^2 = .518) and the recognition test procedure ($F_{(1:126)}$ = 142.291,MSE = 154.485 p < .0005, partial η^2 = .552) confirming the occurrence of a RIF effect in both experiments. This effect was compared using a mixed ANOVA test which revealed that there was no significant main effect of test type ($F_{(1:126)}$ = 0.379, MSE = 1876.677 p < .539 partial η^2 = .158) and no significant interaction between test type and the RIF effect ($F_{(1, 126)}$ = 3.02, p = 0.085).

Table 3.1 Mean % (±SD) of correctly recalled exemplars during the final phase for both tests.

RIF type	Retrieval Practice Status			
	R+	Rp-	Nrp	RIF effect
Category cue	84.3(16.1)	34.5 (20.0)	53.1(17.6)	18.6 (9.7)
Recognition	92.9 (12.4)	55.9(14.6)	68.0 (19.8)	12.1 (15.2)

ANOVAs were conducted to examine facilitation (difference between the percentage recall for Rp+ and Nrp items) and inhibition (difference between the percentage recall for Rp- and Nrp items) in the final recall test. The results of this analysis showed that the facilitation effect of practice was significant for category-cued RIF, $F_{(1:33)} = 52.641$,MSE = 72959.559 $p < .0005$, partial $\eta^2 = .651$with participants demonstrating a greater recall of Rp+ items than Nrp items. The facilitation effect of practice was also significant in the recognition experiment with greater recall of Rp+ items than Nrp items, $F_{(1:26)} = 89.269$, MSE = 7518.382, $p < .0005$, partial $\eta^2 = .737$.

Table 1.2 shows the correlations between the scores obtained with the two test types. The correlation was significant indicating that a high or low RIF effect found using the category cued test procedure is consistent with the RIF effect found using the recognition test procedure. Therefore indicating that the RIF effect may be consistent over time.

Table 3.2 *Correlations between the retrieval practice scores obtained with the two test types.*

	Rp+	Rp-	Nrp	RIF
r	.190*	.615**	.311**	.385**

*= significant (p<0.05) ** = Significant (p < .005)

Cognitive measures and smoking in relation to the two test types

Table 1.3 shows mean (± SD) scores obtained in the neuropsychological tests for the entire sample and the number of cigarettes smoked per day. These scores were below the benchmark for the pathological measures and generally the number of cigarettes smoked per day is below average in comparison to the overall population of smokers.

Table 3.3 *Mean (± SD) scores obtained in the neuropsychological tests for the entire sample and the number of cigarettes smoked per day*

	Mean *(± SD) n=127*
BDI-II	9.70 (7.81)
Schizotypy	8.22 (4.08)
RRS	17.81 (12.48)
Mindfulness	61.12 (13.51)
Number of Cigarettes	10.51 (9.24)

A Pearson's correlation analysis revealed no significant correlations between any of the neuropsychological tests and RIF for either test type. Table 1.4 shows the correlations between BDI-II, Schizotypy, RRS, Mindfulness and Number of cigarettes smoked per day and Recognition RIF. There was a weak non-significant association

between the category RIF procedure and the number of cigarettes smoked per day (r = .104, p = .064).

Table 3.4. *Correlations between BDI-II, Schizotypy, RRS, Mindfulness and Number of cigarettes smoked per day and Recognition RIF.*

	BDI-II		**Schizotypy**		**RRS**		**Mindfulness**		**N of cigarettes**	
	r	p	r	p	R	p	r	p	r	p
Category RIF	.074	.205	.077	.141	.042	.320	.013	.443	.104	.064
Recognition RIF	.028	.323	.075	.155	-.023	.345	-.050	375	.027	.331

To control for any possible effect that neuropsychological function and number of cigarettes smoked per day may have had on the RIF effect an ANCOVA analysis was conducted for each test type and the different measures. However no significant effects emerged see table 1.5. This demonstrates that the RIF effect found using each test type cannot be attributed to the potential impact that, BDI-II, schizotypy, RRS, Mindfulness and number of cigarettes smoked per day may have on the RIF effect.

Table 3.5.*ANCOVA analysis controlling for the neuropsychological tests and number of cigarettes smoked per day in both the category cued and Recognition RIF procedures.*

	BDI-II		Schizotypy		RRS		Mindfulness		N of cigarettes	
	F	p	F	p	F	p	F	p	F	p
Category RIF	.377	.540	.245	.621	.129	.248	.774	.381	.366	.159
Recognition RIF	.177	.675	.421	.518	.679	.412	.127	.723	.119	.731

3.6 Discussion

The aim of the present study was to examine whether the RIF effect is a consistent measure when tested on different occasions and with different procedures. The results of the study revealed that both RIF testing procedures produced a significant RIF effect. This finding contrasts with the previous literature which has argued that the category cued procedure is subject to correlated cost benefits issues as the category cued procedure does not control for output interference (Anderson, et al., 2003). Moreover this study provides support for many studies which have been criticised on the basis that category cued testing at final test does not control for output interference and therefore may contribute to the failure to find impaired RIF in populations that should have impaired RIF, (Conway, M.A. and Fthenaki, 2003; Ford, et al., 2004; Moulin, et al., 2002; Nestor, et al., 2005; Zellner and Bäuml, 2005). However some research has indicated that output interference and RIF probably arise from the same inhibitory mechanism (Bauml and Hartinger, 2002), so the

elimination of output interference may place an unnecessary constraint on the data obtained.

The present study also revealed that the category cued procedure produced a stronger RIF effect when looking at the mean percentage RIF effect scores indicating that the strength of the RIF effect is more apparent using the category cued procedure. It is possible that the reduced RIF effect found using the recognition procedure may be caused by the fact that output interference is controlled for. Anderson and Levy (2007) argued that the best way to control for the correlated costs-and-benefits problem is to use a cue-independent final test, but the data produced here suggests that the RIF effect may be a constant measure and if an individual displays either a high or low RIF effect using one procedure it is possible (likely) that they will produce a similar high or low RIF effect using another RIF assessment procedure. This was demonstrated by the correlation of the RIF effect for the category cued and the recognition test procedure in this study.

However this finding is not consistent with Potts, et al., (2010) as they did not find the same level of consistency between the RIF effect of category-stem cued test and recognition test RIF procedures. They did however find a significant correlation for the category cued procedure when using the same test items, which is consistent with the findings of the present study. Thus to some extent this study provides further

support to suggest that the category cued RIF procedure is a significant and reliable measure of the RIF effect. This is a novel finding which contradicts previous research arguing that category cued testing is subject to output interference and correlated cost benefit issues therefore not a good measure (Anderson, et al., 2000). Although the current findings are consistent with that of Bauml and Hartinger, (2002), who reported that controlling for output interference may be unnecessary and could potentially rule out any effect or RIF that may be present.

However this study was inconsistent with previous findings and possible explanations are necessary as to why the present study found a correlation in the RIF effect over time while Potts, et al., did not. Firstly Potts, et al., conducted the re-test after a delay of one week. It could be argued that one week is not sufficient enough as a procedural practice effect may have occurred, that is for participants may have remembered the structure of the task and thus focused on certain aspects more than others leading to compromised findings. In the current experiment however, a period of three months delay was allowed to control for practice effects. It is also possible that the failure to find the reliability in the RIF effect could be attributed to the significantly smaller participant sample in the Potts, et al., study (n=37) compared to the current study which had a much larger sample of participants (n=127).

Nevertheless it must be borne in mind that the findings from this experiment do not provide evidence for test-retest reliability as different procedures were employed. Therefore a direct comparison of the two different RIF paradigms cannot be made using a different procedure, although the correlations reported here do suggest that the RIF effect may be a reliable finding. However this study provides strong evidence to suggest that the test type employed may not be necessarily as important as has been previously reported (Anderson, et al., 1994, 2003). These findings are consistent with the argument made by Storm and Levy (2012) suggesting that researchers should divert the attention from disentangling the inhibitory and interference accounts of RIF and focus on the function of inhibition on real life situations.

This study also incorporated additional cognitive measures to investigate the association between cognitive functioning and the RIF effect, however no significant association was found between any of the neuropsychological measures and the RIF effect in either the recognition or the category cued procedure. There is evidence that mood is negatively associated with the RIF effect as discussed in the introduction. Groome and Sterkaj (2010) found that the RIF effect was significantly reduced in individuals suffering from clinical depression, this finding was consistent that of Bauml and Kuhbandner (2007) who reported that the RIF effect was significantly reduced in dysphoric members of the normal population (i.e., normal participants subjected to mood induction techniques). Therefore the present study is not consistent with these findings. However the non significant association between

these cognitive functions and the RIF effect might be attributed to the overall low mean scores on these measures which could mean that the scores were not powerful enough to be associated with the RIF effect. For instance the mean (± SD) BDI-II scores were 9.70 (7.81) and the mild depression or low mood mark is 11 therefore it is plausible that the effect of this measure was not sufficient to impact on the RIF effect.

Also the schizotypy questionnaire produced very low scores, the mean (± SD) was 8.22 (4.08) again indicating a plausible explanation in that there was not a strong enough effect to emerge as an association with the RIF effect. It would be interesting for example to conduct a similar analysis with a sample producing a wider distribution of SPQ-B scores. It is also important to note that as smoking has been identified as an important factor in mediating RIF controlling for smoking in future experiments may provide useful. Furthermore it is also possible that the sample recruited may have not provided true responses due to peer pressure as the experiment was conducted in a class setting or perhaps fear of revealing possible abnormalities to their tutor although they were assured that the data would remain anonymous. It is also possible that the lack of motivation to engage with the study may have elicited inaccurate responses; this may be possible due to the fact that the study was conducted as part of a course credit scheme therefore attracting more individuals that may not have had an actual interest in the study.

3.7 Conclusion

This chapter addressed controversies in the current literature regarding the different RIF testing procedures by providing evidence that regardless of the test procedure employed RIF is a robust finding. That is individuals who demonstrate a high RIF effect employing the category cued RIF testing procedure also demonstrate a high RIF effect when employing a recognition RIF testing procedure. The correlation between these scores provided evidence to suggest that the RIF effect is a consistent measure over a period of three months, indicating that the RIF effect may be a reliable finding. This is a novel finding in that to date no study has conducted such investigation, and has important implications for past and future research.

That is this study provides evidence to suggest that the category-cued procedure is an effective measure of RIF and this provides support for studies that have made use of this procedure but have been criticised on the basis of not controlling for output interference. Evidence is also provided for the idea that RIF testing procedures may not be as important as had initially been suggested, as the RIF effect scores on the category cued procedure significantly correlated with the RIF effect scores on the recognition recall procedure. However the category cued recall has been previously found to be a reliable measure over time. Therefore this procedure was used in the subsequent series of studies for this thesis to explore association with depression, schizophrenia and a twin population.

Chapter 4

Retrieval Induced Forgetting in Clinical Depression

4.1 Introduction

This chapter will outline an investigation that examines retrieval induced forgetting in a clinically depressed sample in comparison to healthy controls. The focus of this chapter is on the cognitive functioning of this population and the impact of mood and smoking in relation to the RIF mechanisms. The introduction comprises three main sections: 1) a definition of depression and its significance are discussed; 2) a general review of cognitive functioning in depression is outlined; 3) the significance of Retrieval Induced Forgetting and other mediating factors associated with depression are discussed. Following the introduction, a study of RIF in a sample of sixty five depressed patients and sixty five healthy controls is described.

4.2 Definition and significance of depression in relation to RIF

Depression is characterised by cognitive impairment (slowed reaction time, poor concentration and memory), dysfunctional thoughts (e.g. inappropriate guilt, worthlessness, and suicidal ideation) and biases in attention and interpretation (Mathews and MacLeod 2005). The core symptoms of major depression (MD) are

persistent depressed mood or anhedonia (i.e. loss of pleasure in normal daily activities), appetite disturbance or weight change, loss of libido, sexual dysfunction, non-localized pain, low energy, altered sleep–wake cycle, daytime fatigue and cognitive impairment (WHO 2012). Indeed, disturbances of sleep have been linked directly to cognitive impairment (Harris 2009). These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide, a tragic fatality associated with the loss of about 850 000 lives every year (WHO, 2012). Depression is among the most prevalent of all psychiatric disorders. Recent research has reported 15% of the UK population will experience a clinically significant episode of depression at some point in their lives (GallupWell-Being group 2011).

Depression is frequently co-morbid with other neuropsychiatric and physical difficulties, most often with anxiety disorders, but also with cardiac problems and an increased prevalence of smoking (Carney and Freedland 2009). A large body of literature has demonstrated that depression adversely affects the quality of interpersonal relationships and, in particular, relationships with spouses and children (Gotlib and Hammen, 2009). Not only is the rate of divorce higher among depressed than among non-depressed individuals (Wade and Cairney 2000), but children of depressed parents have also been found to be at an elevated risk for

psychopathology (Joorman, et al., 2008). Also adverse childhood experiences have been described as one of the major environmental risk factors for depressive disorder (Aguileraa, Ariasa, Wichersa, Vidala, Moyaa, Van Os, 2009). Thus exploring the underlying mechanisms associated with this condition is important in order to provide a greater understanding of the cognitive aspects of depression.

Depression is a highly recurrent disorder and over 75% of depressed patients have more than one depressive episode, often relapsing within two years of recovery from a depressive episode (Boland and Keller 2009). Between one-half and two-thirds of people who have ever been clinically depressed will be in an episode in any given year over the remainder of their lives (Kessler and Wang 2009). This high recurrence rate in depression suggests that there are specific factors that increase people's risk for developing repeated episodes of this disorder. Therefore improving the understanding of underlying mechanisms in depression will enhance the knowledge of factors which affect the onset, maintenance and course of depression, potentially leading to a reduction in its prevalence.

There is a long history of research investigating the interaction of cognition and emotion in depression. Clinicians and researchers alike have focused on cognitive processes and on the content of depressive cognition in trying to gain a more comprehensive understanding of the disorder. Biases in cognitive processes such as

attention and memory may not only be correlates of depressive mood; they may also play a critical role in increasing individuals' vulnerability for the first onset and recurrence of depression (Gotlib and Joormann 2010). The following section will review some of the main theories and research findings relating to cognitive and biological functioning in depression.

4.3 Theoretical approaches to depression

4.3.1 Cognitive theories

Cognitive theories of depression suggest that people's thoughts, inferences, attitudes, and interpretations, and the way in which they attend to and recall events, can increase their risk for the development and recurrence of depressive episodes. In respect of this view, three cognitive mechanisms have been implicated in the link between biases in attention and or memory processes and the dysregulation of emotion that characterises depression. These are biased inhibitory processes and deficits in working memory (Joormann 2005); ruminative responses to negative mood states and negative life events (Nolen-Hoeksema 2000); and the inability to use positive and rewarding stimuli to regulate negative mood (Joormann and Siemer 2004, Joormann, et al., 2007).

Cognitive theories propose a vulnerability-stress hypothesis arguing that the onset of depression is due to the interaction of a psychological or biological vulnerability (certain cognitions or particular ways of processing information) and a precipitating stressor (a negative life event or some other environmental factor). Importantly, one of the most effective interventions for depression, Cognitive Behavioural Therapy, focuses on modifying biased interpretations and dysfunctional automatic thoughts (Beck, 1976) and proposes that changes in cognition is a vital step to improving the disorder.

Beck's (1976) theory was one of the most influential theories in cognitive psychology. Beck's theory postulated that existing memory representations, or schemas, lead individuals to filter stimuli from the environment, such that their attention is directed towards information that is congruent with their schemas. Beck theorised that the schemas of depressed persons include themes of loss, separation, failure, worthlessness, and rejection; consequently, depressed individuals exhibit a systematic bias in their processing of environmental stimuli or information that is relevant to these themes. Depressed people attend selectively to negative stimuli in their environment and interpret neutral and ambiguous stimuli in a schema-congruent way maintaining the cognitive triad (negative view of world, oneself and the future). It is also possible that this bias in cognitive processing is associated with inhibitory deficits and a subsequent inability to suppress negative thoughts.

Recent research has demonstrated that inhibitory dysfunction is present in depression, and that this deficit is likely to be valence-specific (Palazidou, 2012). However, whether valence-specific inhibitory deficits are associated with increased negative cognition and whether such deficits are specific to depression remains unclear (Lau, Christensen, Hawley, Gemar and Segal, 2007). The authors posit the theory that inhibitory dysfunction may influence the degree to which activated self-schemas result in the production of depressive cognition. Lau, et al, found that these impairments correlated with self-report measures of negative thinking and rumination.

Research suggests that recurrent ruminative thoughts that occur in response to experiencing negative life events or dysphoric mood states are a core element in the development, maintenance, and recurrence of depressive episodes (Nolen-Hoeksema, Wisco, and Lyubomirsky, 2008,). Despite substantial evidence for the detrimental effects of rumination, however, it still remains unclear what differentiates individuals who are prone to ruminate from those who find it easy to disengage from negative thoughts when experiencing negative mood (Zetche, D'Avanzato and Joormann, 2012). To answer this important question, it is essential to gain a better understanding of the cognitive mechanisms underlying rumination. Several researchers have argued that deficits in attentional control may underlie increased

vulnerability to rumination (Joormann, 2010; Koster, De Lissnyder, Derakshan and De Raedt, 2010). Koster and colleagues (2010), for example, posit that rumination is based on an inability to disengage attention from negative material. According to the authors, self-reflective ruminative thoughts are initiated when individuals experience a discrepancy between their desired goals and the actual situation.

Indeed, there has been growing evidence that depression is characterised by impaired inhibition (Goeleven, De Raedt, Baert, and Koster, 2006; Joormann, 2004; Lau, Christensen, Hawley, Gemar, and Segal, 2007) and that these impairments are related to rumination even after controlling for depression (Joormann and Gotlib, 2008). Inhibition, however, is not a unitary construct but a family of functions (Nigg, 2000) operating at different stages of information processing (Hasher, et al., 1999). At an initial stage, inhibition limits the access of information to working memory ("interference control"), and at a later stage, it helps to remove information that is no longer relevant from working memory ("updating" of working memory). In two studies using latent variable analyses, Friedman and others (Friedmann and Miyake, 2004; Miyake, et al., 2000) have in fact demonstrated that interference control, inhibition of prepotent responses, set shifting, and updating are separable inhibitory functions that differentially predict performance on other cognitive tasks.

To date, however, only a few studies have distinguished different components of inhibition in relation to depression or rumination (see De Lissnyder, Koster, Derakshan, and De Raedt, 2010; Joormann, Nee, Berman, Jonides and Gotlib, 2010; Whitmer and Banich, 2007) notably these studies are almost exclusively based on non-clinical student samples or have used neutral stimuli only. It thus remains unclear which components of inhibition are affected in clinical depression and whether depression and rumination are related to impairments in the same components.

Given the distinction in the literature between adaptive and maladaptive forms of rumination (Watkins, 2008), Zetche, et al., (2012) examined how individual differences in inhibitory functions are related to brooding and reflection (Treynor, et al., 2003). The authors found that clinically depressed participants showed significantly reduced interference control of irrelevant negative information compared to controls. The groups, however, did not differ in their ability to discard no longer relevant negative information from working memory. In contrast, rumination was associated with difficulty removing no longer relevant negative material from working memory but not with deficits in interference control. The authors concluded that it is important to differentiate between components of inhibition to gain a better understanding of cognitive mechanisms underlying depression and rumination.

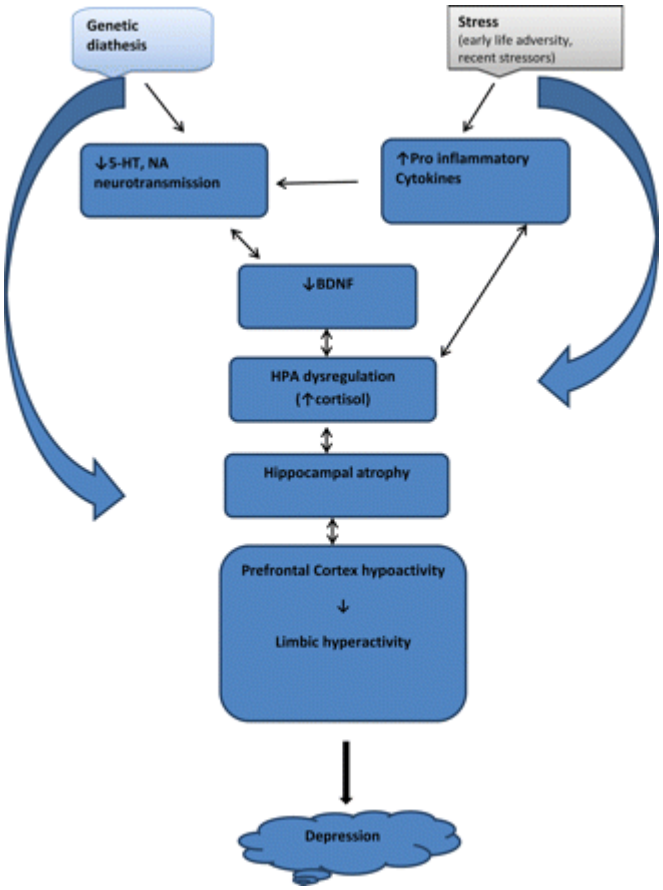
There is evidence suggesting that, at least with respect to memory deficits, depressed individuals might have the ability to perform at the level of non-depressed individuals in structured situations but have problems doing this on their own initiative in unconstrained situations (Hertel 2004). Moreover, these results suggest that eliminating the opportunity to ruminate also eliminated the impairment in the memory task, a result that might explain why unconstrained tasks lead to impaired performance in the depressed group. Unconstrained situations call for cognitive flexibility and goal-oriented behaviour and require cognitive control, that is, focal attention to relevant stimuli as well as inhibition of irrelevant material (Hertel 2004). Thus, these performance deficits in the recall of neutral information do not seem to reflect a generalised deficit or a lack of resources on the part of depressed individuals, but might be due instead to depression-related inhibitory difficulties in the processing of irrelevant information. However this aspect has not yet been investigated using the RIF paradigm.

4.3.2 Cognitive neuroscience approach

A diverse range of theories have been put forward over the past fifty years each one claiming to have the key to the aetiology of depression, based on the narrow perspective of its own discipline (genetic, social, psychological or biochemical). However, in the last decade or so, based on technological advances, major leaps have been made in the understanding of the workings of the brain, particularly, its

significant capacity for plasticity in interacting with the environment (physical and psychological). It has become increasingly clear that both psychosocial and biological factors are highly relevant and far from contradicting each other, they are inextricably linked in the genesis of this multifaceted condition (see figure 4).

Figure 4. 1 Schematic representation of the neurobiology of depression (Palazidou 2012).



A dopamine hypothesis of depression has long been suggested (Janowsky, et al., 1972) arguing that depression is associated with hyperactivation of the cholinergic system and decreased activity of the noradrenergic system.Serotonin and norepinephrine are believed to be key neurotransmitters in the etiology of depression (Robinson, 2007).From the raphe nuclei and locus ceruleus, 5-HT and NE,

respectively, send projections up to the prefrontal cortex and limbic system where emotional depressive symptoms are thought to be mediated (Stahl 2003).Neuroimaging and treatment-based research has focused on serotonergic, noradrenergic and or dopaminergic neurotransmission (Hickie, et al., 2009). Depression has been associated with deficits in 5-HT1A (frontal regions and temporal pole) and in 5-HT2 binding (frontal, temporal and parietal regions) (Bowen, et al., 1989). A substantial body of evidence accrued from animal and human studies indicates that these two monoamine neurotransmitter systems play important roles in both the pathophysiology of depression and the therapeutic effects of antidepressants (Nutt, 2006; Dunlop and Nemeroff 2007).

More recently, the interactions of the various neurotransmitter systems have received increased attention. For instance, via five different postsynaptic receptor types, dopamine has been reported to have both inhibitory and excitatory effects on fronto-subcortical functioning. Dopaminergic connections between the substantia nigra and limbic system play a role in the integration of emotional input and motor activity, cognition and motivation. Both cholinergic and serotonergic systems are involved in the modulation of these dopaminergic pathways (Palazidou 2012). Additionally, glutamatergic corticostriatal and thalamocortical projections, via interactions with both cholinergic and dopaminergic systems, contribute to a negative feedback loop, which serves to limit cortical overstimulation (Tekin and Cummings,

2002). The hippocampus is integrally involved in mood regulation due to its connections to key frontal and subcortical regions including the amygdala, hypothalamus, basal ganglia and PFC. In addition there is evidence to suggest that it plays a direct role in the serotonergic HPA functioning (MacQueen and Frodl, 2011).

Research has documented that a reduced activity in noradrenergic, serotonergic neurotransmission and neurotrophins and hyperactivity of the HPA axis and the inflammatory response system are associated with functional abnormalities.Also structural deficits within the cortico-thalamic-striatal-limbic neurocircuitry disrupt the system balance. As discussed in the general introduction there is evidence that the prefrontal cortex (PFC) is functionally and structurally impaired and unable to regulate the overactivity within the cortical/limbic regions, resulting in the clinical manifestation of the depressive syndrome (Palazidou 2012).

Antidepressant drugs increase monoaminergic neurotransmission and brain-derived neurotrophic factor (BDNF) concentrations and reverse some of the structural changes (at least in the hippocampus, enhancing neo-neurogenesis) and have a beneficial modulatory effect on the disrupted cortico-limbic neurocircuit function (Belmaker and Agam, 2008; Drevets, et al., 2008; Hickie, et al., 2001; Hickie, et al., 1999; Hickie, et al., 2007; Insel, 2009; Krishnan and Nestler, 2010 and Mayberg, 2003). Studies provide further support for the idea that alterations of the cholinergic

system can lead to depressive symptoms and both activation and inhibition of nAChRs may have antidepressant effects through distinct mechanisms (Anreasen and Redrobe, 2009) or through disctinct nAChR subtypes. Numerous clinical and preclinical studies have now established that decreasing acetylcholine transmission at specific nAChRs can positively affect mood and possibly cognitive inhibition and may contribute to the antidepressant effects of nicotine (Picciotto, et al., 2008).

There is evidence that nicotine, a cholinergic agonist, may enhance specific aspects of cognition that require effortful processes (Rusted, et al., 1998; 2000, Edginton and Rusted 2003). Notably nicotine has been associated with increased attentional focus (Wesnes and Warburton, 1984) improved free recall (Warburton and Wesnes 1984; Philips and Fox, 1998) and increased inhibition (Rodway, et al,, 2000; Edginton and Rusted, 2003). It is therefore possible that the retrieval induced forgetting effect is enhanced among smokers due to this positive effect that nicotine has on mood and cognitive inhibition. However this is a complex issue and much research needs to be conducted in order to establish a clear association between RIF, mood, inhibition and nicotine.

4.4 Dysfunctional cognitive processes associated with depression

Inhibition, working memory, and cognitive control are important concepts in understanding dysfunctional cognitive processes that underlie sustained processing of negative information and rumination in depression (Gotlib and Joormann 2010). As discussed in the general introduction working memory is commonly described as a system for the active maintenance and manipulation of information and for the control of attention that are thought to rely on facilitatory and inhibitory processes (Baddeley, 1986). An important characteristic of working memory, and one that differentiates it from long-term memory, is its capacity-limited focus of attention (Cowan, 1995, see also chapter one). Given this capacity-limitation, inhibitory control is critical for updating working memory content efficiently and is therefore essential for engaging in goal-directed planning and for maintaining a coherent stream of thought.

Most contemporary theories postulate that inhibition is not a unitary construct but, instead, involves several components such as response inhibition, cognitive inhibition, and emotional inhibition (Friedman and Miyake, 2004; Nigg 2000). Cognitive inhibition operates at different stages of the processing of information (Hasher andZacks, 1988; Hasher, et al., 1999) for example, by preventing off-goal information from having access to working memory or by reducing the activation of information that was once relevant, but now is irrelevant because of a change in goals.

Studies that have investigated depression-related deficits in tasks that assess various components of working memory have reported few differences between depressed and non-depressed participants on a variety of WM tasks (Channon, et al,, 1993; Oberauer 2005; Baddeley, 2012; Banich 2009). Most of the tasks that are used to assess working memory (e.g. Digit span) involve relatively short retention intervals and, thus, seem to allow a more direct assessment of attention processes irrespective of retrieval from long-term memory. These tasks have been criticised, however on account of the relatively slow presentations that are used to ensure perception of relevant target information. It has been argued that this might allow for chunking and active rehearsal of material and, therefore, might reflect memory deficits rather than deficits in attention (Rokke, et al., 2002). Using an attention blink paradigm that involves rapid serial presentations, Rokke et al., found significant group differences in performance between moderately to severely dysphoric (Beck Depression Inventory scores over 21) and non-dysphoric participants, but only under demanding dual-tasking conditions. It is important to note, however, that only nine moderately to severely dysphoric participants were included in this study, so these findings should be interpreted with caution.

Rose and Ebmeier (2006) reported that depressed patients were slower and less accurate than were controls on an n-back task, but that task difficulty did not influence this effect. These findings replicate results reported by Harvey, et al.,

(2004), who found further that the performance deficit on the n-back task was correlated with number of hospitalisations and with the longitudinal course of the disorder. Importantly, Harvey et al. did not find depression-associated differences on a number of other tasks assessing WM functioning, including a digit span. Consistent with these findings, Egeland, et al., (2003) concluded from the results of their study that reduced performance on WM tasks in depression is due not to a specific deficit in executive functioning, but to a nonspecific reduction in speed and to a loss of vigilance that is consistent with a lack of effort. In line with this Rohlin, et al., (2002) argued that depression has no impact on objective neurocognitive functioning.

Grant, et al., (2001) administered a battery of cognitive tasks to 123 depressed outpatients and noted the surprising absence of cognitive deficits in their sample. The only indications of deficits were fewer completed categories, increased perseveration, and impaired maintenance of set on the Wisconsin Card Sorting Task (WCST), a widely used measure of executive control and cognitive flexibility. These results suggest the operation of depression-related deficits in the generation and maintenance of problem-solving strategies and difficulties in set switching (Harvey, et al., 2004). Importantly, though, there was no evidence of deficits in executive functioning on any of the other tasks administered in this study. Grant et al. concluded that pervasive cognitive deficits most likely characterise elderly depressed

people and severely depressed inpatients who present with psychotic features (Harvey, et al., 2004 and Rose and Ebmeier 2006).

In a recent review paper, Castaneda, et al., (2008) concluded that deficits in certain aspects of executive control and attentional deficits most likely characterise depressed people whereas evidence for learning and memory deficits is more mixed. The authors also highlighted however, that there is significant variability in the extent to which studies report deficits and that this variability is due to the subtype of depression (with deficits being most prominent in psychotic depression) and to the age of the participants (with deficits being most prominent in older depressed adults). Cognitive theories also propose that focusing attention requires individuals to inhibit task-irrelevant thoughts. Thus, the findings reviewed here support the affective interference hypothesis and the proposition that depressed individuals are characterised by reduced cognitive control.

There is mounting evidence however, for biased memory processes in depression (Mathews and MacLeod 2005). Indeed, preferential recall of negative compared to positive material is one of the most robust findings in the depression literature (Mathews and MacLeod 2005, Matt, et al., 1992, Williams, et al., 1997). In a meta-analysis of studies assessing recall performance, Matt and colleagues found that people with major depression remembered 10% more negative words than they did

positive words. In contrast, non-depressed controls exhibited a memory bias for positive information in 20 of 25 studies. It should be noted, however, that memory biases are found most consistently in free recall tasks, and may be restricted to explicit memory.

Watkins (2002) reported that, across studies, no bias is found in depressed participants when the encoding and or the recall of the emotional material depends purely on perceptual processing. For example, if depressed participants are asked to count the letters in emotional words at encoding and to complete word stems or word fragments at recall, no evidence of an implicit memory bias is obtained (Watkins, et al., 2000). If, however, participants are asked to rate the recency of their experience with the word or to imagine themselves in a scene involving the word at encoding, and are asked to freely associate to a cue word or to provide a word that fits a given definition, implicit memory biases are obtained more consistently. Encoding and recall in these latter studies require semantic instead of purely perceptual processing of the material. This suggests that depressive deficits are due in large part to differences in the elaboration of the emotional material.

Depression is associated not only with enhanced recall of negative events, but also with the recall of rather generic memories, despite instructions to recall specific events (i.e., over-generalised memory; Williams, et al., 2007). Autobiographical

memory (AM) is a personal representation of one's past (Conway, M.A. and Pleydell-Pearce, 2000). A generally accepted distinction in AM function is that between semantic and episodic memory or, more specifically, between decontextualised knowledge about an individual's past and event memories situated in a particular time and place (Moscovitch, et al., 2005 and Piolino, et al., 2009). On the autobiographical memory test (AMT), depressed participants respond to positive and negative cues with memories that summarise a category of similar events. Importantly, this research has demonstrated that over-generalised memories are associated with difficulties in problem solving, with deficits in imagining specific future events, and with longer durations of depressive episodes (Raes, et al., 2005).

Research investigating autobiographical memory in relation to depression has consistently demonstrated that depression is associated with over generalised retrieval (Williams, et al., 2007; King, et al., 2010; and Sumner, et al., 2010). When asked to evoke personal memories specifically situated in time and place, individuals with depression tend to recall either personal semantic memories (i.e., general knowledge regarding oneself), extended events that occurred over a period greater than one day or a frequently repeated event (Williams and Dritschel, 1992). Episodic AM has been related to visuo-spatial memory consistent with the concept that retrieval of episodic AM requires vivid revival (or perceptual re-experiencing) of an incident specifically situated in a spatio-temporal context (Moscovitch, et al., 2005;

Svoboda, et al., 2006 and Conway, 2009). In addition, both episodic AM and semantic memory share overlapping activation patterns with working memory prefrontal underpinnings (Burianova and Grady, 2007 and Piolino, et al., 2009). Finally, episodic AM has been only partly related to traditional neuropsychological episodic memory tests and has been consistently dissociated from semantic memory tests (Gilboa, 2004 and McDermott, et al., 2009). A recent study by Semkovska, Noone, Carton and McLoughlin (2012) reported that individuals with depression produced less episodic-specific memories than healthy controls.

Moreover, research has demonstrated that over-generalised memories remain stable outside of episodes of the disorder and have been shown to predict later onset of depressive episodes in postpartum depression (Mackinger, et al., 2000), to predict depression following life events in students and following unsuccessful in vitro fertilization (Minnen, et al, 2005). Brittlebank, et al., (1993) found that over-generalised recall of autobiographical memories, particularly for positive memories, predicted less complete recovery from major depression at a seven-month follow-up assessment. In contrast, Brewin, et al., (1999) found that over-generalised recall of autobiographical memories did not predict recovery from depression, although intrusive memories of life events did predict recovery.

The extent to which individuals retrieve over-generalised memories has been shown to predict delayed recovery from affective disorders (Dalgleish, et al., 2001). Williams (1996)proposed that over-generalised memory is a form of emotion regulation. That is, individuals attempt to minimise negative affect attached to distressing memories by blocking access to details of such memories or by retrieving these memories in a less specific way. Williams, et al., (2007) proposed further that individual differences in cognitive control, and specifically in inhibitory dysfunction, may underlie over-generalised recall in depression.

As discussed above clinical depression is known to be associated with a number of abnormalities of memory and retrieval, which play a part in causing or sustaining depressive mood. These retrieval abnormalities include over-selective memory with a bias to retrieval of distressing events (Bower 1981, Rusting and Dehart 2000), over-generalised retrieval (Williams 1999), and excessive rumination (Nolen-Hoeksema 2000, 2006). It is possible that these retrieval abnormalities may be associated with deficits in cognitive inhibition. Since the mechanism underlying RIF is believed to depend on one of the fractionated inhibitory processes (Anderson 2003), there is a possibility that RIF and other related measures of cognitive inhibition may be associated with these memory abnormalities. The role apparently played by RIF in suppressing unwanted memories raises the possibility that the RIF mechanism could also play a part in suppressing distressing intrusive thoughts,

which are a feature of many psychiatric disorders and are thought to play a role in causing or aggravating those disorders (Lang, et al., 1999).

Retrieval induced forgetting is the idea that recalling information from long-term memory can suppress the accessibility of related representations (Anderson, Bjork and Bjork 1994, see also chapter one). This is an area that has received little or no attention in relation to depression thus far. However evidence suggests that it may be an important underlying mechanism. For example it has been reported that individuals who exhibit an inhibitory deficit are easily distracted by irrelevant information and thoughts, which may result in cognitive deficits and disrupt a coherent stream of thought (Gotlib and Joormann 2011).Indeed, a reduced ability to inhibit irrelevant representations has been proposed as a source of low working memory capacity (Engle, Kane, and Tuholski, 1999).

Moreover individuals diagnosed with current or past major depressive disorder as well as dysphoric individuals, exhibited diminished negative priming (reflecting reduced inhibition) for negative words, compared to participants who had never been depressed (Joormann, 2004 and Goeleven, et al., 2006). Reduced inhibition has also been found to be associated with the tendency to ruminate in response to negative events (Joormann, 2006), suggesting that inhibitory deficits underlie the rumination associated with depression. These studies suggest that inhibitory deficits may play an important role in the onset and maintenance of depression.

Several studies have reported that the RIF effect may be mediated by several factors such as mood (Baulm 2007, Maulds, et al., 2010, Groome and Sterkaj 2010). Studies of depression and dysphoria report that individuals with depression experience broad difficulties involving concentration and memory (Burt, et al., 1995). However it is argued that individuals with depression can easily concentrate on negative self-focused thoughts, and they exhibit enhanced recall of mood-congruent (negatively valenced) material (Mathews & MacLeod 2005). These findings contrasted with Hertel and Gerstle (2003) who reported that dysphoric individuals showed a reduced tendency to suppress item retrieval in the "think/no think" paradigm, in which participants practice suppression of items when paired with certain cues. They found that the dysphoric group produced weaker suppression than did non-dysphoric individuals, regardless of whether the to-be-inhibited items were positive or negative in affect. This may be a further indication of inhibitory deficits in depression.

In line with this a more recent study investigating high and low levels of dysphoria on retrieval-induced forgetting of positive and negative autobiographical memories, has revealed that participants showed facilitation for both negative and positive memories and only showed RIF for negative memories(Harris, Sharman, Barnier and Moulds 2010). The authors attributed this to the differences in baseline memories as participants recalled more positive than negative baseline memories. It was also

found that dysphoric participants showed facilitation for both positive and negative memories; they only showed RIF for negative memories and recall also varied depending on the content of practiced memories and individual differences in anxiety. The authors argued that retrieval-practice might have different outcomes for different kinds of autobiographical memories. These outcomes may depend on individual memory biases and memory valence, and that practicing positive memories may assist mood repair.

There is some evidence however, arguing that RIF may not be associated with low mood. Moulds and Kandris (2006) investigated the strength of the RIF effect in a sample of university students, using the Beck Depression Inventory (BDI) to divide their sample into a high-dysphoric group and a low-dysphoric group. The RIF procedure included both depression-related items and neutral items. Moulds and Kandris found no difference between the RIF scores of the high and low dysphoric groups for either the suppression of the depression-related or the neutral items. It is important to interpret this finding with caution as it involved a normal student sample, and it is plausible that the range of dysphoric students may not have been sufficient enough to establish an association with the RIF effect. Indeed more recently Bauml and Kuhbandner (2007) have reported that the RIF effect was in fact significantly reduced in dysphoric individuals, but again their study was carried out on healthy participants whose mood state was manipulated by mood-induction techniques.

However a very recent study (Ines and Brennen, 2012) reported a RIF effect for neutral material but not for emotional material in a sample of victims of sexual assault. Indicating that RIF may be a selective inhibitory process, which is evidence in line with the idea that individuals with depression have a reduced RIF effect.

Only a few studies have investigated RIF for emotional material, and the findings are as yet inconclusive. For instance, Barnier, Hung, and Conway, M.A. (2004) found RIF for positive, negative and neutral autobiographical memories and a smaller RIF effect for the neutral words, whereas Wessel and Hauer (2006) used positive and negative autobiographical memories as stimuli, and reported a RIF effect only for negative memories. Dehli and Brennen (2009) investigated RIF for words of positive, neutral and negative valence. Using both response time and accuracy as dependent variables, RIF was observed for neutral words but not for either negative or positive words. The findings summarised here suggest that an association with RIF and depression has not been clearly established, some findings suggest that there is an association while others argue that there is not. There is however sufficient evidence suggesting that depression may be associated with inhibitory mechanisms. There has only been one published study (Groome and Sterkaj 2010) investigating RIF in clinical depression, which has indicated that a population of clinically depressed patients showed an abnormal RIF response, thus further exploration is warranted.

Although causality is difficult to establish it is possible that a weak RIF mechanism could be associated with, or is one of the causes of depression.

Aims

The primary objective of the current study is to examine the retrieval induced forgetting effect in individuals with clinical depression and to establish whether this effect is different in comparison to healthy controls. It is also aimed to investigate the relationship between cognitive functioning and the RIF effect to establish whether RIF impairment is associated with global or specific cognitive deficits. The study will also investigate whether inhibitory processes that underlie RIF are modulated by smoking status mood and/or schizotypy in a clinically depressed population and a healthy control comparison.

It is likely that the RIF effect will be impaired in the clinical sample considering that an initial study has reported this effect and there is evidence that depression is associated with a number of abnormalities of memory and retrieval. It is possible that these retrieval abnormalities may be associated with deficits in cognitive inhibition. It is therefore hypothesised that the RIF effect will be reduced in clinical depression in comparison to healthy controls. The RIF effect has been associated with negative memories and with low mood, it is therefore predicted that low mood will be associated with a reduced RIF effect in both patients and controls. Evidence has

also shown that nicotine enhances the RIF effect thus it is predicted that smoking status and the number of cigarettes smoked per day will enhance RIF in both patients and controls.

4.6 Methods

Design

There were three main stages of investigation in this study:

iv) A between-group analysis of patients and healthy control participants. This analysis was implemented to evaluate whether there were significant differences in the RIF effect between the patients and controls.

v) A within-group analysis of the patients and controls (separately) designed to identify and determine the strength of associations between the RIF effect and other cognitive performance measures in each separate group.

vi) A Within-group analysis of the entire sample combined. The comparison made on the basis of scores obtained by all participants on a carefully designed battery of cognitive tests and the RIF paradigm to establish whether the RIF effect is closely associated with other cognitive variables.

Participants

Two groups of participants were tested; a sample of individuals with depression and a sample of healthy controls; demographic characteristics are shown in table 2.1.

Patients

The clinical sample comprised 65 individuals (32 male and 33 female) with a single diagnosis of unipolar depression. This sample was recruited through a local mental health organisation known as MIND, which is an independent registered charity offering a range of services and provides mental health information for anyone living in the local area. Diagnostic criteria were checked in the case notes prior to testing and only patients whose diagnosis was unipolar depression were recruited. The diagnosis was made by a Psychiatrist who was independent of the present study. The clinical status of all participants was stable, the duration of the disorder varied from two to twenty years and they were all on typical prescribed antidepressant medication. Ethical approval was obtained from the NHS Central Office for Research Ethics committee (COREC) and approval was granted from the Chief executive of MIND.

Recruitment of patients

The researcher regularly attended four different drop-in centres, speaking to potential participants individually (see general methods chapter). The study was

explained to each interested participant in detail and an information sheet (see appendix 2) was provided for them to take away and consider whether they wished to participate. The majority of participants consented to participate following the explanation by the researcher. A suitable appointment was arranged for the researcher to attend the centre and conduct the study.

The other means of initial recruitment involved displaying a poster at the centre along with possible appointment times. As there were a number of tests involved in this study, IQ (WASI) testing was carried out on a separate day thus each participant was tested on two occasions. The second appointment was generally arranged at the end of the first testing procedures. All testing took place individually in a quiet room within one of the four MIND centre premises. In agreement with all participants and the MIND centre manager, a donation was made to the MIND organisation, to thank the centre's staff and the participants for their support.

Healthy control participants

There were 65 healthy control participants (35 males and 30 females), who were similar to the patient group in terms of age, sex and level of education in years. The healthy control sample was recruited through different social organisations, including sports and parenting clubs. The healthy controls were screened for any psychopathology by the BDII-II and were asked to report any history of mental

illness. The three percent of the healthy controls that reported taking medication only reported taking an oral contraceptive. If participants in the control condition reported a BDI-II score of over the 11 mark they were not excluded from the study but the results were more closely monitored.

Recruitment of the healthy controls

Different social organisations were approached in order to gain permission to recruit participants for the study. The majority of control participants were recruited from an organisation constituting mainly parents / grandparents and carers of a local under 10s football team. Interested individuals were given information sheets outlining the study and also contained the researcher's contact details. Having been part of this group for over five years the researcher was well acquainted with the participants and vice versa. The participants were given the option to either be entered into a prize draw to win an 'IPod touch' or to receive a high street gift voucher as a token of appreciation for their support on this study. The gift vouchers were distributed at the end of the second experimental procedure whereas the draw took place upon completion of all data collection (July 2011).

Inclusion criteria for both patients and controls requested that participants spoke English as a first language due to the nature of the RIF materials used in this

research. The material contained in RIF were typical English word pairs that a non native English speaker may have not previously encountered i.e. names of birds. Only participants whom successfully completed all stages of the research and in the case of the healthy controls those who did not report a history of any mental illness were included. As a result two people from the clinical sample and one person from the healthy control group were excluded from the analysis.

There were no significant differences between the groups in either age (t = 2.046, p = .120), years of education (t -.829, p= .160), nor smoking status (χ^2 = .278 p=.598). However there were more men in the control group (55.2%) when compared to the number of men in the patient group (39.4%), nevertheless this difference was not statistically significant (χ^2= .277 p=.599).

Table 4.1: *Demographic characteristics of participants*

	Depression (N = 65)	Control (N = 65)
Smokers (%)	49	45
Mean Number of cigarettes smoked per day (± SD)	13.9 (15.44)	12.0 (15.02)
Age (mean years ± SD)	46.4 (± 10.13)	42.4 (± 12.07)
Educ (mean years ± SD)	12.7 (± 1.22)	13.4 (± 1.72)
Sex		
Male	32 (49%)	35 (54%)
Female	33 (51%)	30 (46%)
Anti-psychtotic medication	95.4%	na
Illness duration (mean years ± SD)	11.7 (9.23)	na

Materials

Materials used were, the RIF task, the Ruminative Response Scale, the Mindfulness Scale, the Hopkins Verbal Learning task, the Beck Depression Inventory (II), the brief Schizotypal Personality Questionnaire and a measure of IQ. A description of these measures is outlined in the general methodology section. Each of these was provided on paper but the RIF task was a computerised programme (see general methodology section for full description).

Procedure

Testing took place individually in a quiet room and participants were allowed to take a break at a convenient point in the session if required. All the patients were tested at the MIND centre, whereas some of the controls were tested in their own home and some were tested in a private room at the club. Some participants required help typing the responses due to lack of computer skills (during the RIF task) but had no problems completing the questionnaires although the researcher was present throughout to address any issues or concerns. The study was conducted in two separate phases over different days.

In phase one RIF testing took place, on a specially computerised programme involving four separate phases: *(i) Learning*: participants were shown all 36 category-word pairs one at a time in random order. Each pair was presented for five seconds, and participants were asked to remember as many words as possible. *(ii) Retrieval practice*: participants were required to retrieve nine exemplar words in response to a cue consisting of the category word and the first two letters of the exemplar (e.g. Fruit-Ap). These nine practised items comprised half of the exemplars from half of the category lists.

Participants were allowed 10 seconds to complete each exemplar. Each pair appeared three times, at regularly spaced intervals. *(iii)Retention interval:* this consisted of a 20 minute filled time interval, during which participants completed questionnaires, relevant to the study. *(iv)Retrieval test:* participants were shown each of the category names one at a time, and were allowed 30 seconds to list as many exemplars of each as possible.

The second phase of the study involved testing the same participant on a different day to avoid testing fatigue. In this phase the WASI was conducted followed by the answering of any questions or concerns.

4.7 Results

The Retrieval Induced Forgetting Effect

Between-group analysis of patients and healthy control participants

The correct percentage mean (± SD) recall in the retrieval practice phase for the depression sample was 94.4 (± 8.79) and 94.8 (±7.66) for the healthy control group; this difference was not significant between the groups (t = .276, p = .783). Independent ANOVAs were conducted for facilitation (difference between the percentage recall for Rp+ and Nrp items) and inhibition (difference between the percentage recall for Rp- and Nrp items) in the final recall test. Table 2.2 shows the correct percentages recall and standard deviations in the final recall test for each group and practice condition.

Table 4.2: Mean % (±SD) of correctly recalled exemplars during the final phase.

	Retrieval Practice Status		
	R+	Rp-	Nrp
Depression	81.54 (16.23)	34.87 (21.86)	45.68 (17.96)
Controls	86.15 (15.72)	24.78 (18.51)	51.88 (16.29)

The results of this analysis showed that the facilitation effect of practice was significant for patients, $F_{(1:64)} = 206.463$, MSE = 579.015 $p < .0005$, partial $\eta^2 = .763$ with patients demonstrating a greater recall of Rp+ items than Nrp items. The inhibition effect of practice was also significant for patients demonstrating greater

recall of Nrp items than Rp- items F(1:64) = 16.633, MSE = 6444.563, p<.0005, partial η^2 = .206.

The analyses in the control group yielded an identical pattern of performance for facilitation and inhibition. The facilitation effect of practice was significant in healthy controls recalling more Rp+ items than Nrp items, $F_{(1:64)}$ =227.085, MSE = 880.624, p < .0005, partial η^2 = .078. Healthy controls also showed significant inhibition effects of practice demonstrating greater recall of Nrp items than Rp- items $F_{(1:64)}$ = 156.782 MSE = 55568.562, p < .0005, partial η^2 = .710.

In order to examine if the forgetting effects were similar for the two groups, the data was combined into a mixed design ANOVA. This analyses yielded a significant main effect of inhibition $F_{(1:128)}$ = 289.503, MSE = 55376.187, p < .0005, partial η^2 = .693. There was no main effect of patient and controls $F_{(1:128)}$ = 641.069, MSE = 303893.637, p < .0005, partial η^2 = .834. However there was a significant interaction between patient / control and inhibition score $F_{(1:128)}$ = 14.528, MSE = 2778.846, p < .05, partial η^2 = .102, with a greater inhibition effect in the control group than in the depression group (t = 5.076, p < .0005), indicating that although both patients and controls demonstrated a RIF effect; this RIF effect is less evident among the patients.

Between-group analyses (patients vs controls): neuropsychological tests

A one-way ANOVA was performed with group as a between-subjects factor to determine whether there were significant differences in performance across the tests. The mean performance of the patient group fell below the controls on every measure. To control for the possible confounding effects of age, sex and years of education, an ANCOVA was also performed (see Table 2.3). Patients underperformed the healthy controls on all cognitive variables.

Table 4.3: *shows the mean (± SD) scores and significance level of the different neuropsychological measures, mood and schizotypy tested in both the depression and the healthy control groups.*

	Depression (n=65)	Controls (n=65)	ANCOVA*	
	Mean (± SD)	Mean (± SD)	F	(p)
RRS	36.24 (10.70)	7.20 (6.33)	89.971	(< .0005)
SPQ-B	11.69 (3.84)	4.49 (3.50)	32.664	(< .0005)
BDI-II	23.25 (10.55)	9.20 (7.28)	20.207	(< .0005)
HV- L	23.72 (4.34)	24.06 (4.54)	.777	(=542)
HV- D	9.22 (1.58)	9.28 (1.68)	.504	(= 733)
HV - R	5.85 (2.33)	10.03(1.39)	36.183	(< .0005)
Mindfulness	48. 66 (9.58)	60.4 (13.47)	8.320	(< .0005)
IQ	101.44 (5.07)	102.06 (5.08)	.180	(= 948)
Cigarettes per day	13.86(15.20)	12.00 (15.02)	.787	(=536)

*Controlling for age, sex, and years of education

Pearson's correlations shown in Table 2.4, revealed that in the entire population of this research sample (n=130) the majority of variables significantly correlated with

the RIF effect. IQ scores and number of cigarettes smoked per day were exceptions of this for the entire group. The RIF effect negatively correlated with BDI-II, RRS and SPQ- B, thus the higher the scores on these measures the lower the RIF effect indicating that individuals with lower RIF scores showed greater tendency to depression, rumination and schizotypy. All three elements of the HVLT task and the Mindfulness scale positively correlated with the RIF effect, indicating that the higher the scores on these measures the stronger the RIF effect.

Exploring these variables more closely in each of the experimental groups revealed differential effects for each group (see table 2.4). In the depression sample smoking status was positively correlated with the RIF effect i.e. the RIF effect was greater in smokers. The number of cigarettes smoked per day however did not significantly correlate with the RIF effect in neither the depression sample nor the healthy controls. The Learning and the Delayed Recall elements of the Hopkins Verbal Learning task positively correlated (i.e. the higher the scores on these measure the greater the RIF effect) with the RIF effect in the depression group but not the healthy controls. BDI-II, SPQ-B, RRS, Hopkins Recognition Recall, Mindfulness and IQ did not correlate with RIF effect in neither the depression nor the healthy control sample. In the control population only the learning element of the Hopkins verbal learning task significantly correlated with RIF scores while all other measures remained non-significant.

Table 4.4: *Pearson correlations neuropsychological measures, mood, schizotypy and smoking status in the entire population, the depression sample and the control sample in relation to RIF.*

	Entire population (130)		Depression (n=65)		Control (n=65)	
	r	p	r	p	r	p
BDI-II	-.328**	.001	.022	.859	.027	.831
SPQ-B	-.415**	.000	-.174	.166	.105	.406
RRS	-.529**	.000	-.082	.515	-.180	.152
HV- L	.232**	.007	.270**	.030	.215*	.085
HV- D	.185*	.013	.295*	.017	.174	.167
HV - R	.395**	.002	-.148	.238	.013	.916
Mindfulness	.188*	.013	.-048	.703	-.135	.284
IQ	.034	.913	.074	.805	-.050	.693
Smoking	-.054	.446	-.243*	.043	.024	.851
Cigarettes per day	.196	.024	.128	.309	.197	.116

** = Significant (p < 0.01) * = significant (p< 0.05)

Stepwise linear regression analyses

Analysis of whole sample

The scores for the neuropsychological measures that were shown to be correlated ($p<0.1$) with the RIF effect were entered as independent variables into a stepwise linear regression analyses, age, sex and years of education were entered as covariates. A significant model emerged ($F_{(1,128)} =30.480$, $p<0.0005$) explaining 26% of the variance (Adjusted $R^2 = .265$) in RIF. The Hopkins Verbal Learning and clinical status (depression group or control group) were the strongest predictors of the RIF effect but all other variables were excluded from the regression. When the factor of patient/control group status was omitted from the regression RRS (β = .209, p< .005) HVLT-L (β = .209, p< .005)and cigarettes smoked per day (β = .185, p< .05) emerged as significant predictors of the RIF effect.

Table 4.5: *The unstandardised and standardised regression for the variables entered into the regression model explaining variance in RIF scores (n = 130).*

Variable	B	SE	B	p
HVLT-L	1.014	.597	.209	.001**
RRS	-.340	.205	-.269	.000***
Cigarettes per day	.261	.109	.185	.017*

*= significant (p<0.05) ** = Significant (p < .01) ***= Significant (p < .001)

To thoroughly explore any possible associations a separate regression was run in split groups (patients and controls) but a weaker model was produced therefore the results of these were omitted as the value of the model was strongest in both groups

combined. Exploratory analysis reported in the Pearson correlation revealed that many of the neuropsychological measures significantly correlated with the RIF effect. However exploring these variables in a covariate matrix revealed multicollinearity of factors. Thus Stepwise regression was selected as the most sophisticated statistical method to check for this.

4.8 Discussion

The results of this study revealed that when compared with healthy control participants, the patients showed significant deficits in the RIF effect. These findings are consistent with other studies of RIF in relation to depression and low mood (Groome and Sterkaj 2010; Harris, et al., 2010; Bauml and Kuhbandner2007). However other studies have not found an association between low mood and RIF (Moulds and Kandris (2006). It is possible that this discrepancy in findings may be due to the fact Moulds and Kandris tested a non-clinical sample and the range of dysphoric students may not have been sufficient enough to establish an association with the RIF effect. Also from the current study it emerged that both patients and controls demonstrated the expected standard pattern of recall in a standard category cued RIF paradigm of Rp+ >Nrp>Rp- so it is possible that the same was the case among the dysphoric groups in Moulds and Kandris' study, thus accounting for the non significant difference among their samples. The literature in this field is limited but the current findings further extend the field by providing evidence from a clinical population which are consistent with more recent work.

The significant correlations found when groups were collapsed but not when the clinical and healthy control groups were separated suggests that there may be statistical power issues in split groups of 65 in each condition. The significant correlation in the entire groups (table 4.4) provides further evidence to suggest that RIF is a robust phenomenon associated with many neuropsychological functions, mood, smoking and schizotypy. A salient novel finding, critics may argue that collapsing the data creates limitations in terms of population type, reducing the ability to generalise these findings. However a significant association found in this 'non-ideal' sample makes the evidence stronger and sets foundation for further study.

Mood and Nicotine in Relation to RIF and cognitive functioning

A central finding emerging from this study is the mediating effects that smoking and low mood have on RIF. These are factors that have been largely ignored in previous literature. This study documents that it is possible that the controversies surrounding inconsistent findings using different RIF procedures (see chapter 3) and other RIF studies could be explained by taking into account these mediating factors. For instance some studies have reported that individuals with dysphoria demonstrate a reduced RIF (Bauml and Khusbander, 2007), whilst others have found that only emotional material reduces RIF but not neutral stimuli (Ines and Brennon 2012). Barnier, Hung, and Conway, M.A. (2004) found RIF for positive, negative and neutral autobiographical memories and a smaller RIF effect for the neutral words, whereas

Wessel and Hauer (2006) used positive and negative autobiographical memories as stimuli, and reported RIF effect only for negative memories.

Dehli and Brennen (2009) investigated RIF for words of positive, neutral and negative valence. Ines and Brennen (2012) suggest that emotional material in general, regardless of valence and previous trauma exposure, is resistant to RIF. This is in line with the results from Moulds and Kandris's (2006). This evidence would indicate that depressive states may also increase resistance to RIF, thus could be a possible explanation for the deficient RIF reported in this study. The findings reported in this chapter suggest that mediating factors should be explored in further studies in order to establish a clear RIF effect.

The results of this study revealed that individuals who smoke demonstrate a greater RIF effect in comparison to those who do not. Importantly the number of cigarettes smoked per day emerged as a significant predictor of RIF in a regression analysis. This result further supports that of Edginton and Rusted (2003) who reported that nicotine, a cholinergic agonist, enhanced inhibition in the RIF paradigm, a finding that is consistent with the known effects of nicotine on inhibitory processes and specific aspects of cognition that require effortful processes (Rusted, et al., 1998, 2000). Also as nicotine has been associated with increased attentional focus (Wesnes and Warburton, 1984), improved free recall (Warburton, et al., 1986; Philips and Fox, 1998), and increased inhibition (Rodway, et al., 2000; Edginton and

Rusted, 2003) this study provides further evidence to suggest that smoking status is a salient factor to consider when investigating RIF.

The present study also found in both patients and controls that mood as measured by the BDI-II is negatively correlated with RIF. However BDI-II did not emerge as a significant predictor of RIF in the regression analysis, possibly due to the fact that its effect may have been mediated by rumination scores, which did emerge as a significant predictor of the RIF effect. Reduced inhibition has also been found to be associated with the tendency to ruminate in response to negative events (Joormann, 2006), suggesting that inhibitory deficits underlie the rumination associated with depression. This is in line with Nolen–Hoeksema's work (2000, 2006), who reported that depression is associated with high level of rumination.

The results of this study also revealed that there were significant differences in performance across the range of neuropsychological tests conducted in this study. The mean performance of the patient group fell below the healthy controls on the majority of measures. This finding is consistent with previous research in that individuals with depression have been reported to have impaired cognitive function(Gotlib and Joormann 2010; Beck 1976; Siegle, et al., 2002; Watts and Sharrock 1985; Burt, et al., 1995; Mathews & MacLeod 2005; Harvey, et al., 2004 and Rose and Ebmeier 2006). These findings are important as the neuropsychological measures employed in this study were found to be associated with RIF, therefore providing evidence to support the idea that RIF may be an

important underlying mechanism in depression. Therefore improving the understanding of this mechanism should enhance the current understanding of cognition in clinical disorders.

However a recent study by Ines and Brannen (2012), has suggested that the general cognitive functioning of individuals with depression is not impaired. This may be a possible explanation for the fact that the patient and healthy controls did not significantly differ in the IQ scores in this study. Again this is evidence suggesting that RIF may be a more specific inhibitory mechanism impaired in clinical samples that is independent of general cognitive functioning. Little empirical support has been found so far for depressive deficits in the processing of neutral information. In a series of studies exploring RIF, Joormann (2004) demonstrated that dysphoric participants and participants with a history of depressive episodes exhibit reduced inhibition of negative material that they were instructed to ignore. This clearly indicates that RIF may be an important underlying inhibitory mechanism in depression. It is also important to keep in mind that it can be difficult to differentiate between cognitive deficits and a lack of motivation that often characterises depressed patients (Scheurich, et al., 2008). This study employed neutral material in a category cued recall, it is therefore possible that a there is depression-related impairment in the recall of neutral information.

However the link to low mood suggests that there may be a spiral of events whereby negative emotions induce negative moods that are maintained by rumination. As

outlined in the introduction, the literature suggests that depression is not associated with differential activation levels of negative, compared to neutral, stimulus representations (Castaneda, et al., 2008; Watkins, 2002; Williams, et al., 2007; van Minnen, et al., 2005). Instead, malfunctioning inhibitory mechanisms in the processing of negative stimuli might explain the observed difficulties in disengaging attention from negative material and, consequently, the increased elaboration of negative material that is associated with this disorder.

There is indirect evidence for inhibitory deficits using findings from general research on memory and attention in depression. However evidence clearly suggests that inhibitory deficits are related to impairments in memory and to cognitive biases in depression. However, all of the tasks that have been employed to test this assess a multitude of processes and therefore do not directly address the question of whether depression is characterised by inhibitory deficits. However, a number of experimental methodologies have emerged that have the potential to test inhibition models in that they provide data that cannot be easily explained without a concept like cognitive inhibition. Thus employing a RIF paradigm whilst monitoring mediating factors is important in establishing whether cognitive inhibition is impaired in clinical depression.

Inhibitory processes are clearly an aspect to be investigated particularly in relation to potential enhancement as nicotine, via cigarette smoking has been suggested to

play a role in enhancing inhibition (Edginton and Rusted, 2003). The results of this study provide further support for this and suggest that if inhibition can be potentially enhanced with nicotine, it may also be possible to enhance suppression of intrusive negative thoughts associated with depression and reduce rumination (Nolen-Hoeksema, 2000, 2006). Depression may present cognitive difficulties in suppressing ruminative thoughts. This is similar in individuals with schizophrenia as depression is believed to be closely associated with schizophrenia and therefore may account for the inability to suppress voices, hallucination and thought disturbances. This aspect will be further explored in chapter five. The results of the present study provide a further contribution in understanding cognitive elements of depression.

The primary novel contribution provided by this study is the exploration of the RIF paradigm in a statistically powerful sample of clinically depressed participants. To date the findings in this field are limited and somewhat contradictory or inconclusive. Barnier, Hung, and Conway, (2004) found RIF for positive, negative and neutral autobiographical memories and a smaller RIF effect for the neutral words in healthy individuals. These findings provide evidence for idea that the RIF effect is associated with mood. Thus RIF may potentially be associated with either or both cause and maintenance of depression considering that one of the dominant symptoms of depression is low mood. Similarly other findings (Wessel and Hauer, 2006) reported

RIF for negative memories whilst other reported RIF for only neutral words (Dehli and Brennen, 2009). However, it was unclear whether RIF was associated with depression or low mood from the previous findings but this study provides evidence of a clear/strong association. Therefore indicating that RIF mechanisms may be a central target to explore in order to increase the understanding of depression.

4.9 Conclusion

The results of this study suggest that the RIF effect may be underlying factor associated with depression. This may have important clinical implication in terms of designing interventions to modulate this mechanism. However more research needs to be conducted to thoroughly explore the biological and cognitive processes that are associated with RIF, depression and specific clinical disorders. Also the possible mediating factors identified in this study, such as nicotine enhancing the RIF effect suggest that manipulation of the cholinergic system with nicotine may play a potential therapeutic role in disorders such as depression and schizophrenia. Finally low mood was found to be associated with depression and schizotypy indicating that depression and schizophrenia may be on a continuum of closely associated impairments and exploring inhibitory mechanisms in both disorders will provide a richer and more comprehensive understanding of cognitive functioning of these disorders. Thus the next chapter will explore RIF in individuals with psychosis.

Chapter 5

Retrieval Induced Forgetting in Schizophrenia

5.1 Introduction

This chapter will outline an investigation that examines retrieval induced forgetting in psychosis, with a particular focus on schizophrenia. The focus of this chapter is on cognitive functioning in schizophrenia and the impact of mood, and smoking in relation to the RIF mechanism. The introduction comprises three main sections: 1) A definition and outline of schizophrenia, 2) The significance of smoking in enhancing cognitive functions in schizophrenia. 3) A general review of cognitive functioning in schizophrenia. Following the introduction a study of RIF in a sample of thirty four individuals with schizophrenia and thirty four healthy controls is described.

5.2 Definition of schizophrenia

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) defines positive and negative symptoms of schizophrenia which are present for a period of at least between one and six months. In this regard positive refers to the presence of active symptoms including delusions and hallucinations. Negative symptoms refer to a loss, typically of emotion, speech or

motivation. The DSM-IV-TR describes several sub-types of schizophrenia: including, ‘disorganised’, ‘catatonic’, ‘paranoid’, ‘residual’, and ‘undifferentiated’.

There are also other psychotic disorders listed that resemble schizophrenia but have their own distinct diagnostic criteria e.g. ‘schizophreniform’, ‘schizoaffective’, and ‘psychosis not otherwise specified’. In these disorders illness severity exists on a continuum from mild to severe and diagnostically can sometimes be difficult to distinguish from bipolar disorder which is characterised by similar positive and negative symptoms (Tandon and Carpenter 2012). The history of psychiatric research in schizophrenia and the psychoses is filled with widely accepted aetiological and pathophysiological theories that were eventually disproven. Perhaps no disorder has been more challenging in this regard than schizophrenia.

An assumption of the main diagnostic systems such as the DSM-IV-TR or the International Classification of Diseases, 10th edition (ICD-10) is that psychosis is a categorical entity involving a qualitative change from normality to illness, However, this view has been challenged for epidemiological, experimental, and theoretical reasons supporting the idea that psychotic symptoms may be distributed along a continuum (Van Os, 2001; Van Os, et al., 2009; (Tandon and Carpenter 2012). There are currently many aetiological hypotheses, many of which are encompassed in the neurodevelopmental theory of schizophrenia. This theory postulates that

aetiologic and pathogenic factors occurring long before the formal onset of the illness (probably in gestation, during adolescence and neural reorganisation) disrupt the course of normal neural development, resulting in pathological alterations of specific neurons, and the circuits they form, ultimately resulting in malfunction (Weinberger, 1987; Murray and Lewis 1987; Bloom 1993, and Lewis 1997; Lewis, et al., 2005; Stephan and Friston and Frith 2009; Whitford, Mathalon, Kubicki and Shenton 2012).

These neurodevelopment aberrations do not immediately cause clinical manifestations of the disorder such as those that occur in other neurodevelopmental disorders like autism, fragile X or Down's syndromes (although subtle behavioural, cognitive, and motor precursors have been described); rather, they usually present after a latency period of one to three decades (Smeets, et al., 2012). The proximal events that trigger the formal onset of the illness are not known but are thought to include normal neurobiological maturational processes (e.g., neuronal and glial proliferation and migration, axonal and dendritic proliferation, programmed cell death (apoptosis), axonal myelination, synaptic pruning) and environmental interactions, including exposures to gestational disruption like trauma, stress, infection, and substance abuse (Kushima, et al., 2012; Torrey, et al., 2012; Nielsen and Meyer 2012).

Schizophrenia has been argued to run a progressive course, this has been well documented over the years (Kraeplin, 1919; Huber, et al., 1980; Pfohl and Winokur, 1982; McGlashan, 1988; Davies 1994; Walker, et al., 2004; Rabinowitz, Levine, Haim and Häfner 2007; Ziermans, et al., 2012) currently affecting 1% of the world's population. However it is not clear as to when the illness actually begins, although characteristically the onset of diagnosable schizophrenia is in the late adolescent and early adult periods of the life cycle. The earlier manifestation of the disorder, where symptoms may be less severe, fleeting or transient has been described as the pre-morbid period (Olesen and Parner 2006; Dawson, et al., 2012). It has been suggested that prior to the onset of their psychosis, individuals with schizophrenia exhibit characteristic schizotypal or schizoid personalities and asocial behaviours (i.e., they have social relational impairments). While some patients have these characteristic features, the proportion is relatively small i.e. less than 10% of people diagnosed with schizophrenia (Kraeplin 1919; Huber, et al., 1980; Pfohl and Winokur 1982; Marneros, et al., 2012) .

Schizotypy is the putative genetic vulnerability to developing schizophrenia spectrum pathology without developing full phenotypic expression (Meehl, 1962). Just as schizophrenia is a heterogeneous construct, schizotypy has a broad range of positive and negative symptoms and also contains disorganization traits (Raine & Benishay, 1995). Research has demonstrated that schizotypal personality is more

common in the biological relatives of schizophrenia patients, than in the general population, supporting the notion that these behavioural features are in the "schizophrenia spectrum" (Kendler and Diehl 1993; Nielsen and Meyer 2012).

It has been convincingly demonstrated that patients who subsequently developed schizophrenia had lower scores on measures of social, motor, cognitive, and motor function, and more physical signs of abnormality than normal comparisons. Less than a third of patients exhibit physical anomalies however (Green, et al., 1994; Nielsen and Meyer 2012), and the magnitude of the performance deficits (social, cognitive, and motor) are modest, such that the scores of the vast majority of persons who go on to develop schizophrenia are within the range of the normal comparison group (Done, et al., 1994; Jones, et al., 1994; Nuevo, et al., 2012). Thus, the majority of patients who develop schizophrenia are, for the most part, normal in appearance and behaviour until they exhibit prodromal or formal psychopathological signs of the illness.

A general review of cognitive functioning in schizophrenia

Memory impairment is one of the most reliable and well documented neuropsychological findings in schizophrenia. Almost all schizophrenia patients demonstrate some measure of decline from their expected level of neurocognitive

function (Keefe, et al., 2005). Indeed, it has been frequently shown that patients with schizophrenia perform poorly on immediate and delayed verbal learning tasks, such as the Rey Auditory Verbal Learning Test or the Wechsler Memory Scale (Alemanet, al., 1999; Heinrichs and Zakzanis, 1998; Cirillo and Seidman, 2003). Patients with schizophrenia are sensitive to interference and contextual change between learning and recall and the degree of memory impairment has not been found to be related to medication or duration of illness (Sevan-Schreiber, et al., 1996; Torres, et al., 2004). It seems that patients within the schizophrenia spectrum are compromised in their ability to disregard irrelevant information. This observation is supported by findings demonstrating that patients with schizophrenia produce less release from proactive interference and show a usually high intrusion error rate of items from earlier sets (Chan, et al., 2008)

The findings in the literature thus far suggest mild to moderate deficits in encoding and a moderate to severe deficit in retrieval of episodic memory in schizophrenia (Minzenberg, et al., 2009). A less extensive body of evidence (Mortiz and Mass 2011) suggests normal forgetting on the short-intermediate term (minutes/hours) and abnormal recall of remote memories (months/years). Neurocognitive impairment is a core feature of schizophrenia, and not simply the result of the symptoms or the current treatments of the illness (Greenet, al., 2004). Neurocognitive deficits are the single strongest correlate of real-world functioning (Green, 1996), and are currently

viewed as potential targets for treatment in patients with schizophrenia (Hyman and Fenton, 2003).

As discussed impairments in certain cognitive functions, such as working memory, are core features of schizophrenia. Individuals with schizophrenia have difficulty ignoring irrelevant targets (Park, Püschel, Sauter, Rentsch, and Hell, 2002), and to suppressing prepotent responses (Weisbrod, Kiefer, Marzinzik, and Spitzer, 2000). This is an important real world application as it is generally accepted that suppressing irrelevant memories, thoughts or mental images plays an important role in everyday life. The symptoms that characterise schizophrenia may potentially be explained by inhibitory deficits in mental representations. For example, auditory hallucinations and unwanted intrusive thoughts are closely related however individuals with schizophrenia may have difficulty in identifying unwanted intrusive thoughts therefore progression in hallucinations occurs (Badcock, Waters, and Maybery, 2007; Morrison, 2001.

It has also been found that individuals who experience auditory hallucinations have also more intrusive thoughts than patients who do not hallucinate (Morrison and Baker 2000; Smeets, et al., 2012). It has been argued that hallucinations maybe related to an inhibitory dysfunction, which results in the emergence of redundant or irrelevant material from long-term memory into awareness (Hemsley 2005). If individuals with schizophrenia have difficulties in inhibiting mental events, then

intrusive, repetitive, or unwanted memories will continuously interfere and intrude into consciousness. In this sense, inhibitory impairments in memory could explain the intrusive nature of hallucinations in schizophrenia and have also been linked to thought disorder.

5.4 The role of Retrieval Induced Forgetting in relation to schizophrenia

The role played by RIF in real-life settings remains uncertain, but Anderson and Neely (1996) suggest that RIF might assist the selective retrieval of a required memory by suppressing competition from rival memories. For example retrieving information from a particular category (e.g. a friend's phone number) can induce forgetting of related information within that category (e.g. another phone number), whilst information from an independent category remains unaffected (one's groceries). This view receives some support from Groome and Grant (2005) who found that individuals showing a weak RIF effect report more memory failures in everyday life i.e. people who were found to have a reduced RIF effect were more likely to report being unable to locate their car keys or remote control.

Further evidence for the importance of RIF in real life is demonstrated through cognitive disorders, Calev (1996) found that individuals with schizophrenia reported more negative effect words and overall demonstrate a poorer memory performance

and rate of forgetting; it is possible that impaired RIF may play a crucial part in real life in terms of preventing the inhibition of these negative words.

Further connections between reduced RIF effect and everyday cognitive functioning are found in mood and depression. Bauml (2002) found that induced negative mood in individuals produced a significantly reduced RIF effect. Therefore indicating that mood may play an important part in modulating this mechanism. This is an important implication highlighting that the RIF paradigm can be modulated; raising the possibility that a deficiency in the mechanism underlying RIF might be associated with schizophrenia, since one of the symptoms of schizophrenia is a tendency to suffer low mood or depression.

Further evidence supporting the role of mood/depression in the modulation of RIF was provided by Groome and Sterkaj (2010) who found that there is a significantly reduced RIF effect in individuals with depression in comparison to healthy controls. The authors also reported a significant positive correlation between BDI scores and RIF scores, indicating that high BDI scores significantly reduced the RIF effect, once again highlighting the importance of mood in modulating RIF. Therefore as schizophrenia symptoms are often associated with low mood it is possible that RIF may play an important part in this disorder that is influenced by both mood and psychotic symptoms.

Abnormalities in the cognitive inhibitory functions of individuals with schizophrenia have been reported by several studies (Nestor, et al., 1992; Grunze, et al., 1996, Bauml and Aslan 2004). However these inhibitory abnormalities have not been investigated using the RIF paradigm. The RIF paradigm is of particular interest to the study of associative impairments of schizophrenia because it provides a means to isolate inhibition from other potential mechanisms of retrieval interference in the disease-related associative disturbance (AhnAllen, et al., 2007). Soriano, et al., (2009) reported no significant impairment of RIF in individuals with schizophrenia when using a cued recall procedure at the final test stage, but they found that the schizophrenia group did show a significant RIF impairment when a recognition procedure was used to measure RIF.

These findings appear to suggest that a RIF impairment is found in schizophrenia with some RIF procedures but not with others. Nestor, et al., (2005) investigated the RIF effect in individuals with schizophrenia, but found that they showed a similar RIF response to healthy controls when the word categories were unrelated. In a second experiment using related word categories, they found no significant RIF effect for either the schizophrenia or control group. However, although the schizophrenia group showed no RIF abnormalities, they did show a significant reduction in cued

recall performance for the related but not for unrelated categories, compared with the performance of controls.

In support of the findings by Nestor, et al., (2005), AhnAllen, et al., (2007) reported normal RIF in individuals with schizophrenia when testing for both strong and weak categories. Although their schizophrenia group did demonstrate reduced RIF scores compared to healthy controls, the difference did not reach significance. However, it is important to note that the RIF procedure used in these two studies made use of word-stem cues in the final recall test, in order to control for output interference. This version of the procedure is known to reduce the magnitude of the RIF effect (Anderson, et al., 1994), which may help to explain their failure to detect RIF. In fact recent research has indicated that output interference and RIF probably arise from the same inhibitory mechanism (Bauml and Hartinger, 2002), so the elimination of output interference may place an unnecessary constraint on the data obtained.

5.6 Cognitive enhancing effects of smoking in schizophrenia

There is substantial evidence that neurocognition can be enhanced (Smith, et al., 2002). Studies of the effects of nicotine on persons with ADHD have found that nicotine improves accuracy on neuropsychological measures (Shytle, et al., 2002). Other studies have revealed nicotine-induced reductions in errors of omission and

reductions in the variability of response times (Levin, et al., 1996) demonstrating a beneficial effect of nicotine on sustained attention in patients with ADHD. It has also been found that acute nicotine administration has positive effects on behavioural inhibition in adolescents with ADHD-C (Potter and Newhouse, 2004). However the cholinergic system has been understudied in ADHD and the neurobiological mechanism(s) by which nicotine exerts effects in ADHD are not understood (Potter, et al., 2006).

Edginton and Rusted (2003) provided evidence for inhibitory processes in the RIF paradigm arguing for a more complex subdivision of inhibitory processes, which may be differentially influenced by cholinergic blockade. The authors also found that nicotine, via cigarette smoking, is a modulating factor in RIF as they reported that nicotine can affect task performance by inhibiting unpractised material thereby reducing interference and benefiting the task at hand.

Studies on schizophrenia patients have also revealed positive effects of cigarette smoking or other forms of nicotine administration (patch, nasal spray) on neuropsychological test measures in schizophrenia patients. For example studies showed improved performance scores on cognitive tests in individuals with schizophrenia after cigarette or nicotine administration in pre–post or separate sessions crossover placebo-controlled designs, or better cognitive performance in individuals with schizophrenia maintained on cigarettes compared to those who had

stopped smoking (Georgeet, et al., 2002; Depatie, et al., 2002; Levin, et al., 1996). The cognitive test measures that showed improved performance included, attention and vigilance, spatial organization, measurers of visual–spatial memory (VSWM) and verbal memory.

More recently Sacco, et al., (2005) found that cigarette smoking modifies cognitive deficits in schizophrenia and nicotinic acetylcholine receptors play a role in mediating cigarette smoking–related cognitive enhancement. The authors argued that cigarette smoking may selectively enhance VSWM and attentional deficits in smokers with schizophrenia, which may depend on nAChR stimulation. Individuals with schizophrenia have a higher rate of cigarette smoking than patients with other psychiatric diagnoses or patients without definite psychiatric diagnoses (Dalack, et al., 1998; Glassman, 1993; Kelly. et al., 2012).

In some studies, rates of smoking among schizophrenia patients have ranged from 80 to 90% (Dalack, et al., 1998). The reasons for the widespread smoking behaviour seen in schizophrenia are not well understood but several possible mechanisms have been advanced (Kumari and Postma, 2005). Most of these suggest that nicotine serves as a form of self-medication to reduce the side effects of antipsychotic medications, to enhance the therapeutic effect of antipsychotics and so

alleviate negative symptoms, and/or to ameliorate a number of cognitive deficits associated with schizophrenia.

The self-medication hypothesis (Adler, et al., 1998), proposes that individuals with schizophrenia smoke to cope with unpleasant medication side effects and symptoms, including cognitive deficits (poor attention and thought disorder), and negative (e.g., boredom and anhedonia) or disorganization symptomatology (Aguilar, et al., 2005). Indeed, research has linked smoking to improved cognitive functioning (George, et al., 2006) and decreased negative symptoms (Ziedonis, et al., 1994) in individuals with schizophrenia. However there are inconsistencies in the literature; studies have reported a relationship between smoking and positive symptomatology (Ziedonis, et al., 1994), negative symptomatology (Patkar, et al., 2002), positive and negative symptomatology (Goff, et al., 1992), disorganization symptomatology (Aguilar, et al., 2005), and no relationship with positive or negative symptomatology (Dalack, et al., 1999).

A percentage of patients report, in addition to the 'classic' reasons for smoking reported by healthy smokers, that smoking helps to reduce psychiatric symptoms (Glynn and Sussman, 1990), which some claim become worse during withdrawal (Dalack and Meador-Woodruff, 1996; Glynn and Sussman, 1990). There are few empirical clinical data directly testing these claims, but in one empirical study (Smith,

et al., 2002) smoking high-nicotine cigarettes, compared to smoking de-nicotinized cigarettes, was found to reduce negative symptoms without affecting positive symptoms. Such data primarily describe a therapeutic role of nicotine for negative symptoms of the disorder (e.g. avolition and apathy).

In addition to such clinical aspects, cigarette smoking has also been linked with the familial vulnerability to schizophrenia. It has been hypothesised that smoking may compensate for physiological deficits in schizophrenia deriving from decreases in number or structure, or differences in physiological response, of nicotinic receptors. This may lead to affective and cognitive deficits in schizophrenia patients, and this may be involved as an explanation for the high rate of smoking in schizophrenia (Glassman, 1993). Studies have presented evidence that nicotine administration or cigarette smoking transiently corrects or ameliorates some of the psychophysiological abnormalities found in schizophrenia patients (Adler, et al., 1993; Adler, et al., 1998; Olincy, et al., 1998, Smith, et al., 2005). However the precise role of the cholinergic system in schizophrenia remains controversial.

Further research is required to establish the effects of pharmacological manipulation of the cholinergic system on schizophrenia symptomatology. Also studies need to establish whether putative measures of the cholinergic system are altered in schizophrenia in order to improve the understanding the impact of this system.

Studies examining smoking rates across schizotypy traits have been inconsistent. Some studies have reported a relationship between smoking and some facet of schizotypy and there is also an indication that smoking is associated with an increase of disorganised symptoms (Esterberg, et al., 2007, 2009; Wan, et al., 2008). Research evidence also suggests the relationship between smoking and schizotypy may be associated with increased positive symptoms (Allan, et al., 1995; Joseph, et al., 2003; Burch, et al., 2008; Esterberg, et al., 2007, 2009; Wan, et al., 2007) whilst others argued that it was related to increased negative symptoms (Burch, et al., 2008; Esterberg, et al., 2007).

Several suggestions have been made which attempt to explain these inconsistencies, specifically relating to methodological issues. It has been suggested that studies have employed various measures of schizotypy, which arguably do not measure the full schizotypy spectrum (i.e. positive, negative and disorganization traits). Also some measures have varying relevance to schizotypy (i.e. the psychoticism scale from the Eysenck Personality Questionnaire; Allan, et al., 1995; Joseph, et al., 2003; Burch, et al., 2008). Finally studies have conceptualized schizotypy as a dimensional construct; however, theory and research suggest that it is categorical, with a population incidence of approximately 10% (Blanchard, et al., 2000).

Esterberg, et al., (2007) assessed biological relatives of schizophrenia patients and found that smoking was associated with more severe positive, negative and disorganization traits. Wan, et al., (2008) employed psychometric identification procedures and found that smoking was associated with positive, but not negative or disorganization traits. A more recent study examined smoking in adults with categorically defined schizotypy with a broad range of positive, negative, and disorganization traits and a normative reference group (Stewart, et al., 2010). Stewart, et al, reported that individuals with schizotypy were twice as likely to smoke as individuals in a normative reference group among those with schizotypy, smokers reported more severe disorganisation and less severe negative schizotypal symptoms. These findings offer insight into mechanisms underlying smoking in schizotypal individuals and suggest areas for further research.

5.2 Aims and Hypothesis

The primary objective of the current study is to examine the retrieval induced forgetting effect in psychosis and to compare the strength of this effect to that of healthy controls. This will help to address the current controversies and mixed findings in the literature. It aims to investigate the relationship between cognitive functioning and the RIF effect in a schizophrenia sample in comparison to healthy controls to establish whether a RIF impairment is associated with global or specific

cognitive deficits in this population. The study will also investigate whether inhibitory processes that underlie RIF are modulated by nicotine, via cigarette consumption, low mood and high schizotypy in a schizophrenia sample and a healthy control comparison.

It is likely that the RIF effect will be impaired in the clinical sample as the most recent study employing recognition recall has documented this effect. The evidence reviewed here suggests that schizophrenia is associated with a number of abnormalities of memory and retrieval. It is possible that these retrieval abnormalities may be associated with deficits in cognitive inhibition. It is therefore hypothesised that the RIF effect will be reduced in schizophrenia in comparison to healthy controls. The RIF effect has been associated with negative memories and with low mood, it is therefore predicted that low mood will be associated with a reduced RIF effect in both patients and controls. Evidence has also shown that nicotine has a positive effect on cognitive functioning and in particular it has been found to enhance the RIF effect. Thus it is predicted that the magnitude of the RIF effect will greater among smokers in comparison to non smokers in both patients and controls.

5.3 Methods

Design

There were three main stages of investigation in this study:

vii) A between-group analysis of patients and healthy control participants. This analysis was implemented to evaluate whether there were significant differences in the RIF effect between the patients and controls.

viii) A Within-group analysis of the entire sample combined. The comparison made on the basis of scores obtained by all participant on a battery of cognitive tests and the RIF paradigm to establish whether the RIF effect is closely associated with other cognitive variables.

ix) A within-group analysis of the patients and controls (separately) designed to identify and determine the strength of associations between the RIF effect and other cognitive performance measures in each separate group.

Participants

Two groups of participants were tested: a sample of individuals with schizophrenia and a sample of matched healthy controls; demographic characteristics are shown in table 3.1.

Patients

The clinical sample comprised 34 individuals (22 male and 12 female) diagnosed with schizophrenia. This sample was recruited through a local mental health

organisation known as MIND, which is an independent registered charity offering a range of services and provides mental health information for anyone living in the local area. Diagnostic criteria were checked in the medical case notes prior to testing and only patients whose diagnosis was schizophrenia were recruited. The duration of the disorder varied from two to twenty years. The diagnosis was made by a psychiatrist who was independent of the present study. The clinical status of all participants was stable, they were all outpatients and they were all on antipsychotic medication. Ethical approval was obtained from the NHS Central Office for Research Ethics committee (COREC) and approval was granted from the MIND Chief executive.

Healthy controls

There were 34 healthy control participants (19 males and 15 females), who were matched in terms of age, sex distribution and level of education in years to the patient sample. The healthy control sample was recruited through different social organisations, including sports and parenting clubs. The healthy controls were screened for depression by the BDII-II and were asked to report any history of mental illness including any psychotic disorders. None of participants in the control condition scored over 11 on the BDI-II.

Inclusion criteria were that participants spoke English as a first language due to the nature of the RIF materials used in this research. The stimuli contained in RIF were

typical English word pairs that a non-native English speaker may not have encountered before i.e. names of birds. Only participants whom successfully completed all stages of the research, and in the case of controls who did not report a history of any mental illness, were included. There were no significant differences between the groups in either age (t = .713, p = .478), years of education (t -.375, p= .709), nor smoking status (χ^2 = .381 p=.087). However, there were more men in the patient group (65%) when compared to the control group (55.9%), nevertheless this difference was not found to be statistically significant (χ^2 = .553 p=.310), (See Table 3.1).

Table 5.1: *Demographic characteristics of participants*

	Schizophrenia (N = 34)	Control (N = 34)
Smokers (%)	32.4 %	37.6%
Mean number of cigarettes smoked per day (± SD)	18 (16.93)	8.82(13.59)
Age (mean years ± SD)	43.58 (± 11.9)	41.47 (± 12.47)
Educ (mean yrs ± SD)	13.58 (± 1.20)	13.73 (± 1.94)
Sex		
Male	22 (65%)	19 (55.9%)
Female	12 (35%)	15 (44.1%)
Anti-psychtotic medication	94.1%	na
Illness duration (mean years ± SD)	13.2 (7.86)	na

Materials

Materials used were similar to those in previous studies including, the RIF task, the ruminative response scale, the mindfulness scale, the Hopkins verbal learning task, the Beck Depression Inventory (II), the brief schizotypal personality questionnaire and a measure of IQ. A description of these measures is outlined in the general methodology section. Each of these was provided on paper but the RIF task was a computerised programme (see general methodology section for full description).

Procedure

Testing took place individually in a quiet room and participants were allowed to take a break if necessary. All the patients were tested at the MIND centre and some required help with typing the responses (during the RIF task) and required slightly longer to complete testing in comparison to the controls. Whereas some of the controls, were tested in their own home and some were tested in a private room at the club. The study was conducted in two separate phases over different days. In the first phase the RIF testing took place on a specially computerised programme involving four separate phases: *(i) Learning*. Participants were shown all 36 category-word pairs one at a time in random order. Each pair was presented for five seconds, and participants were asked to remember as many words as possible. *(ii) Retrieval practice*. Participants were required to retrieve nine exemplar words in response to a cue consisting of the category word and the first two letters of the

exemplar (e.g. Fruit-Ap). These nine practised items comprised half of the exemplars from half of the category lists.

Participants were allowed 10 seconds to complete each exemplar. Each pair appeared three times, at regularly spaced intervals. *(iii)Retention interval:* This consisted of a 20 minute filled time interval, during which participants completed questionnaires, relevant to the study. *(iv) Retrieval test:* Participants were shown each of the category names one at a time, and were allowed 30 seconds to list as many exemplars of each as possible. The second phase of the study involved the recruitment of the same participant on a different day to avoid testing fatigue. In this phase the WASI was conducted followed by a full debriefing and answering of any questions or concerns.

5.4 Results

The Retrieval Induced Forgetting Effect

Between-group analysis of patients and healthy control participants

The percentage of correct recall in the retrieval practice phase was 96.3% for the schizophrenia group and 96.7% for the control group; this difference was not significant between the groups (t = .193, p = .473). Different independent ANOVAs were conducted for facilitation (difference between the percentage recall for Rp+ and

Nrp items) and inhibition (difference between the percentage recall for Rp- and Nrp items) in the final recall test. Table 3.2 shows the percentages of correct recall and standard deviations in the final recall test for each group and practice condition.

Table 5.2: Mean % (±SD) of correctly recalled exemplars during the final phase.

	Retrieval Practice Status		
	R+	Rp-	Nrp
Schizophrenia	74.84 (1.82)	29.74 (1.65)	43.95 (1.57)
Controls	85.29 (1.58)	28.43 (2.06)	50.49 (1.62)

The results of this analysis showed that the facilitation effect of practice was significant for patients, $F_{(1:33)} = 52.641$,MSE = 72959.559 $p < .0005$, partial $\eta^2 = .651$ with patients demonstrating a greater recall of Rp+ items than Nrp items. The Inhibition effect of practice was also significant for patients demonstrating greater recall of Nrp items than Rp- items F(1:33) = 62.318, MSE = 15459.559, p<.0005, partial $\eta^2 = .442$.

The analyses in the control group yielded an identical pattern of performance for both facilitation and inhibition. The facilitation effect of practice was significant in healthy controls recalling more Rp+ items than Nrp items, $F_{(1:34)} = 92.269$, MSE =

87518.382, $p < .0005$, partial $\eta^2 = .737$. Controls also showed significant inhibition effects of practice demonstrating greater recall of Nrp items than Rp- items $F_{(1:33)} = 67.343$, MSE = 44136.039, $p < .0005$, partial $\eta^2 = .703$.

In order to examine whether the forgetting effects were similar for the two groups, the data was combined into a mixed design ANOVA. This analyses yielded a significant main effect of inhibition $F_{(1:66)} = 76.984$, MSE = 11184.641, $p < .0005$, partial $\eta^2 = .538$. There was no main effect of patient and controls $F_{(1:66)} = .458$. MSE = 197974.764, $p < .0005$, partial $\eta^2 = .855$ However, there was a significant interaction between group and inhibition score $F_{(1:66)} = 3.599$. MSE = 11184.641, $p < .05$, partial $\eta^2 = .0.52$ with a greater inhibition effect in the control group than in the schizophrenia group ($t = 2.588$, $p < .05$), indicating that although both patients and controls demonstrated a RIF effect; this RIF effect is less evident among the patients.

Between-group analyses (patients vs controls): neuropsychological tests

A one-way ANOVA was performed with group as a between-participants factor to determine whether there were significant differences in performances across the tests. The mean performance of the patient group fell below the controls on every measure. To control for the possible confounding effects of age, sex and years of

education, an ANCOVA was also performed (see Table 3.3). Patients significantly underperformed the healthy controls on the majority of the variables except for the measures of HV-L, HV-D and IQ

Table 5.3: *shows the mean (± SD) scores and significance level of the different neuropsychological, schizotypy, mood and smoking behaviour measures tested in both the schizophrenia and the healthy control groups.*

	Schizophrenia(n=34)	Controls (n=34)	ANCOVA*	
	Mean (± SD)	**Mean (± SD)**	**F**	**(p)**
RRS	5.18 (6.40)	7.70 (6.15)	1.865	(p= .177)
SPQ-B	8.64 (4.64)	3.82 (2.95)	26.139	(p< .0005)
BDI-II	12.76 (12.42)	9.38 (7.36)	2.675	(p = .107)
HV- L	23.05 (4.21)	22.94 (4.65)	.012	(p= .913
HV- D	9.12 (1.67)	8.88 (1.71)	.329	(p= 568)
HV - R	6.79 (2.51)	10.00 (1.30)	43.424	(p< .0005)
Mindfulness	56. 76 (12.43)	61.64 (13.91)	3.329	(p = .132)
IQ	101.76 (6.15)	102.09 (5.89)	.0.49	(p= 825)
Cigarettes per day	17.64 (16.93)	8.82 (13.60)	5.612	(p<.05)

*Controlling for age, sex, and years of education

Within-group analysis of the entire sample combined

Correlations for both groups combined

Table 3.4, shows Pearson's correlations of three main scores, the patient sample, the healthy control sample and the scores for both groups combined. This analysis revealed that when the data for the entire sample was combined the SPQ-B

negatively correlated with the RIF effect ($r = -.242$, $p < .05$), in that the higher the SPQ-B scores the lower the RIF effect. While the Hopkins's Verbal Learning Recognition element positively correlated ($r = .335$, $p < .005$) with the RIF effect i.e. the more items recalled/recognized was associated with a greater RIF effect. This was also the case for the number of cigarettes smoked per day ($r=384$, $p<0.005$), the more cigarettes smoked per day the greater the RIF effect. All the other neuropsychological measures including the BDI-II did not significantly correlate with the RIF effect.

Linear Regression Analysis

The scores for the neuropsychological measures that were shown to be correlated ($p<0.1$) with the RIF effect were entered as independent variables into a stepwise linear regression analyses, age, sex and years of education were entered as covariates. A significant model emerged ($F_{(1, 33)} = 8.823$ $p<0.001$) explaining 29% of the variance (Adjusted $R^2 = .259$). The Hopkins's Verbal Learning recognition element emerged as a significant predictor explaining 25% of the variance (Adjusted $R^2 = .225$). The SPQ-B emerged as a significant predictor explaining 29% of the variance (Adjusted $R^2 = 259$). Number of cigarettes smoked per day also emerged as a significant predictor of the RIF effect explaining 15% of the variance (Adjusted $R^2 = .135$). Indicating that these three predictor variables are the most strongly

associated with the RIF effect in the whole sample, see table 3.4 below for the unstandardised and standardised coefficients of each variable.

Table 5.4: *The unstandardised and Standardised regression for the variables entered into the regression model explaining variance in RIF scores (n = 68).*

Variable	B	SE	β	p
HVLT-R	1.591	.710	.248	.029*
SPQ-B	-.805	.403	-.223	.050*
Cigarettes per day	.418	.110	.404	.000***

*= significant (p<0.05) ** = Significant (p < .01) ***= Significant (p < .001)

Stage 3: Within-group analyses of patients and controls (separately)

Correlations for the patient group

Exploring the data in the patient sample revealed a strong significant positive correlation for the number of cigarettes smoked per day in relation to the RIF effect (r=.604, p<0.001), all the other neuropsychological measures remained non significant. However, rumination scores negatively correlated with the RIF effect (r = - .282, p=.053) although the level of significance was at the borderline level.. All the other neuropsychological measures including the BDI-II did not reach significance for this sample.(See table 2.5 below).

Correlations for both the healthy control and patient group

Exploring the data in the patient sample revealed a strong significant positive correlation for the number of cigarettes smoked per day in relation to the RIF effect (r=.540, p<.005), indicating that the more cigarettes smoked the greater the RIF effect. The mindfulness scores were negatively correlated (r = -.329, p<.05) with the RIF effect in this sample, indicating that the lower the scores on the mindfulness measure the lower the RIF effect. Rumination scores approached borderline significance of negatively correlating with the RIF effect (r = - .279, p=.055), suggesting that lower rumination scores may also be associated with a reduced RIF effect. All of the other measures including the BDI-II did not reach significance for this population see table below.

Table 3.5: *Pearson correlations of neuropsychological, mood, schizotypy, and smoking status measures in separate and combined groups in relation to RIF.*

	Entire sample(130)		Schizophrenia (n=65)		Control (n=65)	
	r	p	r	p	r	p
BDI-II	-.080	.257	-.098	.290	-.092	.303
SPQ-B	-.242*	.023	-.066	.355	-.027	.439
RRS	-.157	.077	-.282	.053	-.279	.055
HV- L	.042	.366	.175	.161	-.041	.408
HV- D	.027	.414	.103	.281	.024	.447
HV - R	.335**	.003	.235	.090	-.016	.308
Mindfulness	-.123	.159	-.060	.368	-.329	.029*
IQ	-.024	.424	-.119	.251	-.034	.425
Cigarettes per day	.384**	.001	.604	.000**	.530	.001**

* = significant (p< 0.05) ** = Significant (p < 0.01)

Stepwise linear regression for the patient group

The analysis in the patient group, revealed a significant effect ($F_{(1,33)}$ =18.340 p<0.001) for the number of cigarettes smoked per day explaining 36% of the variance (Adjusted R^2 = .344) in the RIF effect. The SPQ-B was not found to be a significant predictor of the RIF effect in this model (β = -.070, p =627). The HVL-R also emerged as a non-significant predictor of RIF in this model, (β = -.070, p=.627). Therefore these variables were excluded from the model.

Table 3.6: *The unstandardised and standardised regression for the number of cigarettes smoked per day explaining variance in RIF scores among the patient group (n = 34).*

Variable	B	SE	β	p
Cigarettes per day	.646	.183	.530	.000***

***= Significant (p < .001)

Stepwise linear regression for the control group

Similar to the patient group, the stepwise linear regression analysis for the healthy control group revealed only the number of cigarettes smoked per day was associated with the RIF effect in this sample. The model was significant ($F_{(1,33)}$ =12.474, p<0.005) accounting for 28% of the variance in the RIF effect (Adjusted R^2 = .344), see table 3.7. Mindfulness (β = -.186, p= .242) and Rumination (β -.071, p=.647) did not significantly predict the RIF effect therefore were excluded from the analysis

Table 3.7: *The unstandardised and standardised regression for the number of cigarettes smoked per day explaining variance in RIF scores among the healthy control group (n = 34).*

Variable	B	SE	β	p
Cigarettes per day	.493	.115	.604	.000***

***= Significant (p < .001)

5.6 Discussion

The results revealed that there is a significant RIF effect in both patients and controls. However, in comparison to the controls the patients demonstrated a significantly reduced RIF effect. This pattern is similar to the clinical depression sample indicating that while the level of the RIF effect varies between patients and controls, it is nonetheless evident among the clinical population, thus providing evidence for a robust RIF effect in clinical and non-clinical samples. This is consistent with the previous research (Anderson & Bell, 2001; Bajo, Gómez-Ariza, Fernandez, and Marful, 2006; Little, Storm, and Bjork, 2011; Garcia-Bajos, Migueles, and Anderson, 2009; MacLeod, 2002; Saunders and MacLeod, 2002; Shaw, Bjork, and Handal, 1995; mental imagery, Saunders, Fernandes, and Kosnes, 2009; creative problem solving, Storm, Angello, and Bjork, 2011; autobiographical memory, Barnier, Hung, and Conway, 2004).

These findings suggest that RIF may be associated with some of the symptoms associated with psychosis. In people experiencing thought disorder for example, there may be an inability to inhibit unwanted or irrelevant material. Other symptoms of psychosis such as hallucinations may also arise from the inhibitory deficits. For example, difficulty in identifying unwanted intrusive thoughts was argued to be associated with hallucinations (Badcock, Waters, and Maybery, 2007; Morrison, 2001). If inhibitory deficits are present in psychosis, it is possible that these individuals are not able to identify those thoughts as intrusive, as they are unable to

suppress them. It has also been found that individuals who experience hallucinations have also more intrusive thoughts than patients who do not hallucinate (Morrison and Baker 2000; Smeets, et al., 2012).

It has been argued that hallucinations maybe related to an inhibitory dysfunction which results in the emergence of redundant or irrelevant material from long-term memory into awareness (Hemsley 2005), therefore deficient RIF may be an important factor in maintaining these thought processes. If patients with psychosis have difficulties inhibiting mental events, then intrusive, repetitive, or unwanted memories will continuously interfere and intrude into consciousness. In this sense, inhibitory impairments in memory could explain the intrusive nature of hallucinations in schizophrenia and have also been linked to thought disorder. This is consistent with research reporting individuals with schizophrenia demonstrate less release from proactive interference and high intrusion error rate of items from earlier sets (Chan, et al., 2008).

It is possible that deficient RIF could be accountable for the deficits in encoding and retrieval of episodic memory that have been reported in schizophrenia (Minzenberg, et al., 2009) in that faulty inhibitory mechanism may be an underlying issue. Also it is possible that normal forgetting on the short-intermediate term and abnormal recall of remote memories (Mortiz and Mass 2011) reported in schizophrenia may be

associated with deficient RIF in that information presented may not be accurately encoded due to lack of inhibitory control. Further neurocognitive impairment may also be associated with lack of inhibitory control, and this has been reported as a core feature of schizophrenia (Greenet, al., 2004), thus mechanisms underlying RIF may be implicated in this impairment.

This is in line with literature arguing that individuals with schizophrenia have difficulty ignoring irrelevant targets (Park, Püschel, Sauter, Rentsch, andHell, 2002), and suppressing prepotent responses (Weisbrod, Kiefer, Marzinzik, and Spitzer, 2000), which again may be due to underlying RIF mechanisms. This is an important real-world implication as it is generally accepted that suppressing irrelevant memories, thoughts, or mental images plays an important role in everyday life. The symptoms that characterise schizophrenia could be explained by inhibitory deficits in mental representations that may be associated to RIF impairment found in this study.

This study also revealed the RIF effect is associated with other variables, combining patients and controls into a Pearson correlation analysis revealed that SPQ-B, HVL-R and number of cigarettes smoked per day significantly correlated with the RIF effect. The SPQ-B was negatively correlated indicating that the higher the scores on this measure i.e. higher levels of schizotypy, the lower the RIF effect. Therefore providing evidence for an association of psychosis-like symptoms and the RIF effect. The literature so far has not investigated the impact of schizotypal symptoms in

relation to RIF. Indeed if at risk groups are found to exhibit inhibitory deficits, potential therapeutic interventions focusing on improving inhibition may be beneficial in the prevention of the development of psychosis. This is an area that needs much focus and development, but these findings provide a basis that warrant further investigation.

One possible explanation for the RIF impairment found in schizophrenia patients in the present study is that their RIF scores may have been impaired as a direct result of the schizophrenia pathology, and this raises the interesting possibility that the intrusive thoughts, which frequently characterise schizophrenia may reflect an impairment of a cognitive inhibitory mechanism in these patients. However, an alternative explanation is that RIF scores may have been impaired by depression, a symptom which is often co-morbid with schizophrenia. It has been established that schizophrenia tends to be associated with depression (Bentall, Drake, Haddock, Kinderman, Lewis, Pickles, and Tarrier, 2004; Moser, Krieg, Zhil, and Lautenbacher, 2006; Pickard, Thomson, Evans, K.L. Porteous, and Muir, 2007). Indeed Pickard, et al., (2007) found evidence that schizophrenia and major depression are often associated with the same gene (DISC 1). The co-morbidity of schizophrenia and depression is unlikely in the present study, as the BDI scores of the schizophrenia group were not significantly higher than those of the control group ($t=1.365$, $p=1.77$). This is therefore evidence that inhibitory deficits may be present in individuals with schizophrenia independent of depression.

Rumination was found to positively correlate with the RIF effect in the patient sample and reached near significance for both the control and the patient sample. As rumination and depression are interrelated (Nolen-Hoeksema, 2000, 2006) it is possible that the RIF effect is therefore mediated by mood. The failure in finding a significant association between the RIF effect and BDI in this study could be accounted for by the fact that overall this sample did not have a very high BDI score therefore the low scores of the BDI are not sufficient enough for a correlation to emerge. This is contrary to the findings reported in chapter four in this thesis and previous findings in other populations (Groome and Sterkaj 2010, Bauml and Khusbander, 2007). However there were generally low BDI-II scores (mean 11.07, ± sd 10.27) in the schizophrenia sample, which may be accountable for the lack of significant association in the RIF effect. Also the BDI-II scores did not differ significantly between the groups (t=1.365, p=1.77).

The results of the present study provide support for the findings of Soriano, et al., (2009), who also reported a RIF impairment in schizophrenia, though in their case using recognition cues. However, the present study further advances the current field by confirming that this impairment also occurs when using category cues. There are several possible explanations for the present contradictory findings in the literature. Firstly, Nestor, et al., (2005) and AhnAllen, et al., (2007) used a different version of the RIF procedure to that used in the present study. Both of these studies used a

cued recall procedure as their final retrieval test, whereas the present study used a category cued recall procedure.

It has been established that free recall yields a stronger RIF effect than cued recall (Anderson, et al., 1994), but it also differs from free recall in that RIF scores include an element of output interference. Thus the discrepancy between the findings of the present study, Soriano, et al's., (2009) and those of the two previous studies could possibly reflect the absence of output interference in the schizophrenia group, or it may simply reflect the greater statistical power made possible by the enhanced RIF effect achieved with the procedure used in the present study. Although it must be noted that the findings in chapter three of this thesis indicated that there was no significant difference between the test measures in the overall RIF effect.

A further finding from this study was the emergence of the HVLT-R to be a positive predictor of the RIF effect in the regression model for both groups combined but not in either group in isolation. However this finding indicated that the individuals who were able to suppress interference of similar items when identifying target items had a stronger RIF effect, providing evidence of possible deficient inhibitory processes or an underlying inhibitory mechanism in individuals with schizophrenia. This is consistent with findings that have reported that patients with schizophrenia perform poorly on immediate and delayed verbal learning tasks, such as the Rey Auditory

Verbal Learning Test or the Wechsler Memory Scale (Alemanet, al., 1999; Heinrichs and Zakzanis, 1998; Cirillo and Seidman, 2003). However, the exact association is not clearas this variable was not a significant predictor of RIF when the groups were independently analysed.

An important finding that emerged from the results of this study was the number of cigarettes smoked per day were positively correlated with the RIF effect, the more cigarettes smoked the higher the RIF effect. This finding was further strengthened by the emergence of the number of cigarettes smoked per day as a significant predictor of the RIF effect in a multiple regression analysis. This was the case in a model for both groups combined, for the schizophrenia group alone and for the healthy control group alone. These results provide further evidence for the idea that cognition can be enhanced with nicotine (Smith, et al., 2002).

Also the emergence of number of cigarettes smoked per day as the single most independent predictor of the RIF effect is consistent with studies that have reported nicotine-induced reductions in errors of omission and reductions in the variability of response times (Levin, et al., 1996) demonstrating a beneficial effect of nicotine on sustained attention in patients with ADHD. It has also been found that acute nicotine administration has positive effects on behavioural inhibition in adolescents with ADHD-C (Potter and Newhouse, 2004). However, the cholinergic system has been

understudied in ADHD and the neurobiological mechanism(s) by which nicotine exerts effects in ADHD are not understood (Potter, et al., 2006).

Importantly effects of nicotine on individuals with ADHD have found that nicotine improves accuracy on certain neuropsychological measures (Shytle, et al., 2002).The results of the current study suggest that nicotine does indeed improve neuropsychological performance in both patients and healthy controls. Also the study of Sacco, et al., (2005) found that cigarette smoking modifies cognitive deficits in schizophrenia and nicotinic acetylcholine receptors play a role in mediating cigarette smoking–related cognitive enhancement. The authors argued that cigarette smoking may selectively enhance VSWM and attentional deficits in smokers with schizophrenia, which may depend on nAChR stimulation.

There is also evidence that modulation of the cholinergic system with nicotine, via cigarette smoking can enhance inhibitory processes (Edginton and Rusted 2003, Rusted 2001). However it is not clear why pharmacological manipulation of the cholinergic system with nicotine among individuals with psychosis show improved performance on cognitive measures. The results of the current study provide evidence to suggest that underlying inhibitory mechanisms may be involved. This is an area that needs further exploration.

However these findings have very important implication for RIF research both past and present as it indicates that smoking is an important modulating factor of the RIF effect. Therefore it must be taken into account when investigating RIF in order to correctly interpret the findings. It is also an important and novel finding in that it indicates that pharmacological manipulation of the cholinergic system with nicotine in individuals with schizophrenia can improve their cognitive functioning. This may also apply to other clinical disorders; this has important clinical implications in relation to potential design of therapeutic interventions for clinical disorders.

One potential limitation to the study is that many of the schizophrenia participants were receiving medication for their condition. This was a possible confounding variable, and indeed it has been reported that such medication can affect memory function (Claudio, Soares, and Cohen, 2003). However this is a complex issue as some types of antipsychotic medications improve memory performance while others impair performance and the current sample is limited in that there is no information about the specific medication that the patients were taking. It must therefore be accepted that the data reported in this study could partly reflect the influence of medication, though this limitation will of course apply to almost every study carried out on individuals with schizophrenia. A further consideration is that schizophrenia patients tend to perform poorly on cognitive tests due to their lack of motivation and reduced ability to concentrate. However, this is unlikely to have been a major factor in the present study, as the schizophrenia and control groups did not differ significantly in their Rp+ scores (see table 2.2).

5.7 Conclusion

The finding that RIF is apparent in clinical depression but impaired in comparison to healthy controls suggests that inhibitory mechanisms may be an underlying factor associated with schizophrenia. This may have important clinical implications in terms of designing interventions that may be able to modulate this mechanism. However more research needs to be conducted to thoroughly explore the biological and cognitive associations of RIF and schizophrenia and other clinical disorders. Also the possible mediating factors identified in this study, such as nicotine enhancing the RIF effect suggest that pharmacological manipulation of the cholinergic system may play a potential therapeutic role in clinical disorders. Finally, schizotypy was found to be negatively associated with the RIF effect indicating that depression and schizophrenia may be on a continuum of closely associated impairments and exploring inhibitory mechanisms in both disorders will provide a richer and more comprehensive understanding of cognitive functioning of these disorders. More specifically their underlying genetic factors may be associated with RIF and this has not previously been explored. Thus the next chapter will outline the RIF effect in twins, to explore potential genetic links of inhibitory processes in clinical disorder

Chapter 6

Retrieval Induced forgetting in healthy and schizophrenia twin pairs

6.1 Introduction

This chapter will outline an investigation that examines retrieval induced forgetting in twin pairs. The main aim of the study is to examine whether the RIF effect is a heritable aspect of cognition and if so, the impact that schizophrenia has on the heritability of RIF. The sample consists of twins either concordant or discordant for schizophrenia and twins where neither sibling has a history of schizophrenia. Both sub-samples contain monozygotic and dyzygotic twin pairs. The focus of the chapter is on the cognitive functioning of this population with particular attention on IQ, Verbal Learning, Verbal fluency, Trail making, mood, and smoking in relation to the RIF mechanism. The introduction comprises two main sections: the genetic contribution to the aetiology of schizophrenia, and a general review of on twin studies of cognition.

6.1.1 Genetic contribution to the aetiology of schizophrenia

Twin studies represent a “natural experiment” for examining the contribution of genetic and environmental influences. As identical or monozygotic (MZ) twins have all their genes in common, any difference between members of a pair would

arguably be due to environmental differences. Since fraternal or dizygotic (DZ) twins share only half of their genes, the importance of genetic effects can be estimated by comparing the similarity of identical and fraternal twins. The extent to which MZ twins are different provides an estimate of the importance of “non-shared environments”, which represent those environmental factors that are specific to the individual and cause differences in pairs of individuals (Pedersen, 2000). The most widely researched topic in twins has been the general factor of intelligence, g. This is due to the fact that g contributes to the cognitive domains of memory, executive functions and language. It is also a strong predictor of educational attainment, occupational achievement, aspects of health and health-related behaviour, as well as longevity. As an intelligence phenotype, g has been considered as very stable across decades (Deary, 2008 and Deary, et al., 2009). It is possible that retrieval induced forgetting is associated with heritability and indeed with intelligence. However to date this has not been investigated.

While the genetic influences on g as a general cognitive factor are substantial, the environment would exert a similar and significant amount of influence on cognitive abilities. Environmental influences are divided into shared (common) and non-shared (unique) effects, and the former is considered not as important because of the “equal environment assumption” (McGue and Christensen, 2001) in twin studies. Shared environment refers to common household, family, school, and diet that are assumed to be common between the twin pair. Non-shared environmental influence refers to

individual experiences of one twin that are unique to that twin. While there is evidence that heritability strongly contributes to schizophrenia there is no study investigating RIF, intelligence and other cognitive functions in both healthy and control twins and twins with schizophrenia.

A substantial genetic contribution to the aetiology of schizophrenia has been reported, with heritability estimates in the region of 80–85% (Kendler, et al., 1995; Cardno, et al., 1999; Cardno and Gottesman, 2000). Although the causes of schizophrenia are not completely understood, the importance of genetic factors has been firmly established by family, twin and adoption studies. Over the last decade a large number of linkage and (genome-wide) association studies have been carried out (Cohen-Woods, Schosser, McGuffin2009; O'Donovan, Craddock, Owen 2009). The genes thus far identified only explain a small part of the genetic risk for schizophrenia, although many seem to be involved in neurodevelopmental processes (Harrison 2007; Stevens, Smith, Rash, Vaccarino, 2010; Karlsgodt, et al., 2008). However there are clearly other contributing factors yet to be identified.

There is increasing appreciation for the neurodevelopmental underpinnings of many psychiatric disorders, for instance neural stem cells (NSCs), defined as self-renewing, multipotent cells that are present in both the embryonic and adult brain. Several recent research findings demonstrate that psychiatric illness may begin with abnormal specification, growth, expansion and differentiation of embryonic NSCs (Arnold, et al., 2005; Buckley, et al., 2007; Eisch, et al., 2008; Thomas and

Peterson, 2008; Jaaro-Peled, et al., 2009; Vaccarino, et al., 2009). For example, candidate susceptibility genes for schizophrenia, autism and major depression include the signalling molecule Disrupted In Schizophrenia-1 (DISC-1), the homeodomain gene engrailed-2 (EN-2), and several receptor tyrosine kinases, including brain-derived growth factor and fibroblast growth factors, all of which have been shown to play important roles in NSCs or neuronal precursors (Stevens, Smith, Rash and Vaccarino (2010).This suggests that part of the genetic risk leading to the development of schizophrenia is expressed as abnormal brain development as demonstrated by various reported cognitive deficits and neuroimaging studies.

Although there has been considerable evidence supporting the hypothesis that schizophrenia is a neurodevelopmental disorder, specific inhibitory processes have yet to be investigated. (Fish and Kendler, 2005; Rapoport, et al., 2005 and Weinberger, 1995) This model postulates that schizophrenia is the result of abnormal neurodevelopment, and therefore early signs of the disorder may originate during the prenatal period and continue during infancy and into adolescence (Keshavan, et al., 2008). Some studies have shown a high rate of psychopathology and cognitive difficulties in relatives of schizophrenia patients (Davalos, et al., 2004, Keshavan, et al., 2008, Maziade, et al., 2008 and Niemi, et al., 2003), indicating that cognitive difficulties found in schizophrenia may have a genetic stem.

Further evidence has emerged from studies showing that the risk of schizophrenia increases with the degree of genetic relationship and the number of affected family members. For example, in monozygotic twins the risk for schizophrenia has been estimated around 44%, decreasing to 10% in dizygotic twins and other first-degree relatives, to 4% in second-degree relatives and to 1% in third-degree relatives and the general population (Gottesman, 1994, Risch, 1990 and Ross and Compagnon, 2001). However it has been argued that gene searches have been impeded by the disorder's polygenic inheritance, reduced penetrance, heterogeneity and the illness' non-specific clinical presentation (Gottesman and Gould, 2003; Tan, et al., 2008).

6.1.2 Executive function and cognitive processing in twins

Executive functioning encompasses cognitive functions like selective and sustained attention, working memory, and inhibition. The heritability of executive functioning is of interest because impairment of these functions is associated with several cognitive disorders like ADHD (Barkley, 1997). Neurobehavioral phenotypes (or ‘endophenotypes’) might better characterise the genetic pathways that lead to complex disorders than the behavioural symptoms of pathology. As endophenotypes serve as ‘a genetic guide’ they should be heritable themselves (Gottesman, 1997, Skuse, 2001and Gottesman and Gould, 2003).A small number of studies

investigated to what extent individual differences in executive functioning may be due to genetic variation (i.e., heritability) or environmental variation.

Stins, et al., (2005) investigated processing speed of selective attention and working memory in 5-year-old mono- and dizygotic twin pairs. It was shown that there were familial influences on task performance but no clear distinction could be made between genetic and common environmental influences. For inhibition, as measured with a go-no-go task, and sustained attention in the same 5-year-old twin pairs, Groot, et al., (2004) found genetic influences on both tasks while no significant common environmental influences were present. Polderman, et al., (2006) investigated individual differences in working memory in the same twins as Groot (2004) and Stins, et al., (2005) when they were 12 years old. Variation in indices of working memory was for 43–56% explained by genetic variance. Ando et al. (2001) reported comparable findings in young adults where genetic variance contributed for 43–48% to the variance in WM performance. A further longitudinal study of twins found that genetic variation was the most important explanation for individual differences in executive functioning (Polderman, et al., 2007).

Moreover impairments in selective components of executive function are seen in unaffected family members of patients with schizophrenia and may represent the biological expression of increased genetic risk. However, it remains to be established

whether the covariance of executive impairment with schizophrenia is due to an overlap in genes responsible for both the illness and the neurocognitive impairment, or alternatively whether the covariance is due to common environmental effects (e.g. birth complications). It has been argued that this question can be addressed by using structural equation modelling or genetic modelling in a classic twin design (Rijsdijk and Sham, 2002). Toulopoulou, et al., (2007) applied this method to intellectual functioning and its four indices and episodic memory (Owens, et al., 2011 and Toulopoulou, et al., 2010). The authors found a strong genetic overlap between schizophrenia and IQ, working memory and episodic memory.

Twin studies have reported that cognitive impairments in individuals with schizophrenia appear to be most severe in episodic memory and executive processes (Reichenberg and Harvey, 2007 and Toulopoulou, et al., 2010) specifically the Wisconsin Card Sorting Task (WSCT), verbal fluency (Reichenberg and Harvey, 2007). A meta-analysis by Sitskoorn, et al., (2004) found that unaffected relatives may have similar impairments, with moderate deficits in the TMT part B and mild to moderate deficits in verbal fluency. Furthermore studies of neurocognitive functioning, in the higher risk population have shown poorer neuropsychological performance compared to healthy controls, following a pattern similar to the deficits observed in schizophrenia but with a less severe profile. It has also been found that children at high risk for schizophrenia perform worse on intelligence tests than do

children of non-schizophrenia parents (Ott, et al., 1998). In fact, one long-term study using a range of different intelligence tests (instructions test, verbal analogies, mathematical knowledge and non verbal analogies) observed that more than 28% of those who went on to develop schizophrenia were approximately one standard deviation below the mean of the general population (Reichenberg, et al., 2006).

Heritability of intelligence has been studied extensively, both in adults and in children, but far less is known about the developmental genetics of cognitive abilities. Many behavioural genetic studies yield the largely consistent result that genetic differences account for at least 50% of the observed variability in cognitionin adults (e.g., Bouchard and McGue, 1981; McCartney, et al., 1990; Bratko, 1996; Rijsdijk, et al., 1997, 1998; Alarcón, et al., 1998, 1999, Posthuma, et al., 2000). Individuals with Schizophrenia and their first-degree relatives exhibit impaired working memory performance (Glahn, et al., 2003). Attempts to determine the neural bases of these working memory deficits suggest that reduced efficiency of certain critical neurocognitive inhibitory mechanisms may be involved (Callicott, et al., 2003, Manoach, 2003 and Karlsgodt, et al., 2007).

Studies have also shown higher rates of psychopathology and cognitive difficulties among relatives of schizophrenia patients than among the general population. De la Serna, et al., (2010) investigated the relationship between clinical and

neuropsychological characteristics in children and adolescents at high genetic risk for schizophrenia. The authors tested 26 children and adolescents of first-degree relatives diagnosed with schizophrenia (high-risk, group) and 20 controls whose parents and siblings did not meet DSM-IV criteria for any psychotic disorder. De la Serna, et al., reported that high risk children showed more clinical symptoms and cognitive abnormalities than healthy controls. This evidence suggests that cognitive abnormalities are associated with heritability.

Research has reported that general cognitive ability in relation to heritability increases from around 25% in five to six year olds to 80% in adults (Bartels, et al., 2002, Finkel, et al., 1998 and McClearn, et al., 1997). Heritability estimates for measures of memory performance also suggest that they differ as a function of age, but data are scarcer than for general cognitive abilities. A study in elderly male twin pairs (mean age 71.8 years), showed a heritability of verbal memory of 56 % (Swan, et al., 1999). However it is known that heritability for general cognitive abilities increases across the life-span, in that abilities such as IQ and memory are more likely to be related to heritability in the later stages of development (Plomin, et al., 2001 and Bartels, et al., 2002) therefore heritability of 56% may not be a substantial finding.

6.1.3 Review of Cognitive dysfunction in twins

Most studies have shown deficits in verbal memory and learning in high risk children (Cosway, et al., 2000; Erlenmeyer-Kimling, et al., 2000; Johnstone, et al., 2002; and Schubert and McNeil, 2007), as well as poor performance in working memory, including spatial working memory (Niendam, et al., 2003 and Smith, et al., 2006). Studies have showed high heritability of general memory in young children (Bishop, et al., 1996; Bishop, et al., 2006 and Byrne, et al., 2006). There are a limited number of studies that included a measure of the dynamics during the initial trials of a verbal learning task (e.g. adding and retaining words of a given list into the phonological loop). Van Soelen, et al., (2009) found that differences in verbal learning abilities are moderately heritable in healthy 9-year-old twin pairs and their older siblings.

Significant heritability has been reported at all ages, with an increase of genetic influences and decrease of shared environmental influences over the years (Bartels, et al., 2002). Several studies have also demonstrated attentional deficits in child and adolescent first-degree relatives of patients with schizophrenia (Erlenmeyer-Kimling, et al., 1993 and Keshavan, et al., 2005). Shared environmental influences are responsible for stability as well as change in the development of cognitive abilities, represented by a common factor influencing FSIQ at all ages and age-specific influences (Bishop, et al., 2005). It has been well established that genetic influences

seem to be the main driving force behind continuity in general cognitive ability, represented by a common factor influencing IQ at all ages.

Neuroimaging studies have demonstrated that compared to controls, patients and their non-schizophrenia co-twins exhibit relatively larger changes in the electrophysiological signatures of the stimulus-encoding and memory-consolidation stages of working memory performance, per unit increase in memory demands (Bachman, et al., 2008). However correlational approaches that examine the relation between neuropsychological measures and brain morphology or physiology in schizophrenia twins have yielded inconsistent results. Goldberg, et al, (1994) demonstrated that medial temporal and prefrontal regions are important in the symptomatic expression and cognitive failures of schizophrenia.

Owens, et al., (2011) studied a total of 418 monozygotic and dizygotic twins, including pairs concordant and discordant for schizophrenia. In this study participants completed the Trail-making task part A and verbal fluency tasks to assess initiation, processing speed and strategic processing TMT part B to test attentional flexibility, and the WAIS-III to assess general intellectual function and to investigate whether selective measures of executive processing are genetically linked to schizophrenia and to quantify the genetic (i.e. heritability) and environmental contributions to their variability. Owens, et al., found strong evidence

for the validation of executive impairment as a cognitive endophenotype, independent of age, sex and educational history. The authors also reported that tests of verbal fluency and the TMT scales shared a substantial genetic overlap with predisposition to the disorder. This study also found that verbal fluency and IQ are highly correlated with heritability. This study provides evidence to suggest that a high genetic correlation of schizophrenia disorder and executive dysfunction may also be associated with inhibitory processes. Although some studies have provided evidence to suggest that inhibition as measured by RIF is associated with specific brain region activation there have not been any studies to date that have investigated the RIF effect among twins.

6.2 Aims

The primary objective of the current study was to examine the retrieval induced forgetting effect in monozygotic and dizygotic concordant and discordant schizophrenia and healthy control twins. This was done in order to establish whether the RIF effect is a heritable component and to determine if heritability is comparable between the schizophrenia and healthy control twins. This should aid to increase the understanding of inhibitory processes and the underlying mechanisms associated with RIF. It was also aimed to examine whether heritability was consistent in other cognitive domains. The relationship between cognitive functioning and the RIF effect was investigated to establish whether RIF impairment is associated with global or

specific cognitive deficits in this population. Finally potential mediating factors of inhibitory processes that underlie RIF were investigated specifically, nicotine, and low mood in both clinical and non-clinical twin pairs.

The studies reviewed here suggest that heritability is highly associated with cognitive functioning and it is therefore predicted that the RIF effect will emerge as a stable finding within the twin pairs in both the schizophrenia twins and control twins. However as this is the first study to test twins for the RIF effect no prediction is made in regard to the strength to which the RIF effect corresponds between twins

The evidence reviewed in here and in chapter five suggests that schizophrenia is associated with retrieval abnormalities in memory that may be associated with deficits in cognitive inhibition. It is therefore hypothesised that the RIF effect will be reduced in the schizophrenia twins in comparison to healthy controls. Also a reduced RIF effect has been associated with low mood and negative memories. It is therefore predicted that low mood will be associated with a reduced RIF effect in both patients and healthy control twins. Evidence discussed has also shown that nicotine has positive effect on cognitive functioning and in particular it has been found to enhance the RIF effect. Thus it is predicted that twins who smoke will demonstrate a greater RIF effect.

6.3 Methodology

Design

There were four main stages of investigation in this study:

i) A between-group analysis of monozygotic twins concordant for schizophrenia and healthy control monozygotic twins was conducted. This analysis was implemented to evaluate whether there were significant differences in the RIF effect between the patients and controls. A further analysis was conducted in both of these groups to test for differences within each twin pair to examine heritability.

ii) A between-group analysis of monozygotic twins discordant for schizophrenia with their non schizophrenic twin pair was conducted. This analysis was implemented to evaluate whether there were significant differences in the RIF effect between the probands and co-twins. A further within group analysis was conducted investigating differences with each twin pair to examine heritability.

iii) A Within-group analysis of dizygotic twins was conducted to establish differences in the RIF effect within each twin pair.

iv) Correlation analysis was conducted for each twin group to establish associations between different neuropsychological measures and the RIF effect in each twin pair respectively.

Participants

This study was conducted in association with the Institute of Psychiatry and the Maudsley hospital as part of an ongoing twin's project. Probands with schizophrenia were recruited nationally throughout the United Kingdom from National Health Service treatment centres through referrals by their treating psychiatrist.

Control twins were recruited from a volunteer twin register held at the Institute of Psychiatry, London, England. Exclusion criteria applied to all of the groups were age younger than 18 years, a history of a neurological disorder or of a systemic illness with known neurological complications, a history of significant head injury associated with loss of consciousness for more than 1 minute, and current harmful substance use or dependence (defined as within the last 12 months). No candidate included in the study had a psychotic illness directly attributable to the harmful use of illicit substances. The study was approved by the UK Multicentre Research Ethics Committee and all of the subjects gave written informed consent before participating. Table 5.1 provides demographic characteristics of all patients.

Clinical assessments

DSM-IV diagnoses were made using the Schedule for Affective Disorders and Schizophrenia Lifetime Version (Spitzer and Endicott, 1978), or by using the Structured Clinical Interview for DSM-IV (First, et al., 1997) supplemented by information from medical notes. Zygosity was determined by assessment of 12 highly polymorphic microsatellite markers and a standardized twin likeness

questionnaire (Cohen, et al., 1975). In concordant pairs, both members fulfilled the criteria for DSM-IV schizophrenia or schizoaffective disorder. In discordant pairs, one member was diagnosed with DSM-IV schizophrenia or schizoaffective disorder, whereas the co-twin was free of any psychotic illness. In control pairs, both members were free of personal and family history of psychosis or schizophrenia spectrum disorder. The probability that any of the discordant pairs would become concordant for schizophrenia in the future was low, given that a mean (SD) time of 10.88 (8.70) years had elapsed since the onset of illness in the affected members of the MZ discordant patients and 17.71 (13.19) years in the affected members of

Table 6.1.Demographics means (±SD) for patients, unaffected co-twins and controls.

	MZ CC twin pairs with Sz	**MZ DC twin pairs with Sz**	**MZ DC non psychotic twins**	**MZ control twins**	**DZ control twins**
N	22	11	11	22	22
Age, mean (SD)	49.68 (13.76)	46.40 (9.63)	46.40 (9.63)	43.11 (12.59)	43.11 (12.59)
Sex, male, *N* (%)	7 (26.2)	7 (35.0)	7 (35.0)	92 (63. 9)	90 (76.3)
Education, mean (SD)	12.76 (2.46)	12.15 (2.28)	12.15 (2.28)	13.90 (2.79)	14.65 (2.79)

Abbreviations: CC, concordant; DC, discordant; MZ, monozygotic; DZ, dizygotic.

Material and Procedure

Materials used were, the RIF programme, the BDI-II and the Hopkins Verbal Learning Task (outlined in the general methodology section) and The Trail making task. The Trail making task is in two parts, A and B; in test A circles containing numbers 1 to 25 are distributed along a page, the aim is to connect the numbers in ascending order. In part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the

aim is to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). Participants are timed and instructed to connect the circles as quickly as possible without lifting the pen from the paper. Errors are pointed out and affect the participant's score, in that the correction of errors is included in the completion time for the task.

Testing took place in a quiet room and participants were allowed to take a break if necessary. The study was conducted in a private room at the Institute of Psychiatry.

6.4 Results

ANOVAs for the Retrieval Induced Forgetting Effect in both twin groups

Table 4.2, shows the percentages of correct recall and standard deviations in the final recall test for each group and practice condition. Independent ANOVAs were conducted for facilitation (difference between the percentage recall for Rp+ and Nrp items) and inhibition (difference between the percentage recall for Rp- and Nrp items) in the final recall test for each group. Results for each analysis are outlined under separate headings for the relevant twin group.

Table 6.2: *Mean % (±SD) of correctly recalled exemplars during the final phase for patients, unaffected co-twins and controls.*

	MZ CC twins with Sz (n=22)	**MZ DC twins with Sz (n=11)**	**MZ DC non psychotic twins (n=11)**	**MZ control twins (n=22)**	**DZ control twins (22)**
Phase 2	86.9	91.3	96.7	95.8	97.9
Rp+	72.22 (18.38)	71.71 (20.70)	87.88 (12.62)	87.37 (13.41)	81.53 (16.15)
Rp-	29.29 (19.25)	31.31 (25.24)	23.23 (13.57)	24.74 (14.52)	27.02 (17.01)
Nrp	41.41 (18.75)	42.42 (23.47)	45.95 (12.93)	53.53 (16.13)	63.04 (1.71)

Abbreviations: CC, concordant; DC, discordant; MZ, monozygotic; DZ, dizygotic; Sz, schizophrenia

The RIF effect in MZ CC schizophrenia twins compared to MZ controls

The results of this analysis showed that the facilitation effect of practice was significant for MZ CC twins with schizophrenia $F_{(1:21)} = 31.332$, MSE = 10440.516 $p < .0005$, partial $\eta^2 = .599$ with participants demonstrating a greater recall of Rp+ items than Nrp items. The Inhibition effect of practice was also significant for the MZ CC twins with schizophrenia, demonstrating greater recall of Nrp items than Rp- items $F_{(1:21)} = 14.349$, MSE = 1616.162 , $p<.005$, partial $\eta^2 = .406$.

The analyses in the MZ control twins yielded a similar in results for both facilitation and inhibition. The facilitation effect of practice was significant with greater recall of Rp+ items than Nrp items, $F_{(1:21)} = 89.355$, MSE = 12595.398, $p < .0005$, partial $\eta^2 = .810$. The inhibition effects of practice was also significant, demonstrating a greater recall of Nrp items than Rp- items $F_{(1:21)} = 58.166$, MSE = 9116.162, $p < .0005$, partial $\eta^2 = .735$.

In order to check if the forgetting effects were similar for the two groups, the data was combined into a mixed design ANOVA. This analyses yielded a significant main effect of inhibition $F_{(1:42)} = 259.942$, MSE = 11184.641, $p < .0005$, partial $\eta^2 = .538$. There was no main effect of patients and controls $F_{(1:42)} = .120$. MSE = 197974.764, $p= .913$, partial $\eta^2 = .235$.However there was a significant interaction between patient

/ control and inhibition score $F_{(1:42)} = 5.323$. MSE = 808.081, $p < .05$, partial $\eta^2 = .112$with a greater inhibition effect in the control twins than in the schizophrenia twins ($t = 2.78$, $p < .05$), indicating that although both the MZ CC twins and controls demonstrated a RIF effect; this RIF effect is less evident among the patients.

To investigate if there were differences between the twin pairs a further mixed ANOVA was conducted revealing a significant main effect between twins for inhibition in the MZ CC for schizophrenia twin group ($F_{(1:21)} = 85.908$, MSE = 54994.388, $p<.0005$, partial $\eta^2 = .811$). There also was a significant interaction of inhibition and twin pair grouping ($F_{(1:21)} = 6.059$, MSE = 549.944, $p<.05$, partial $\eta^2 = .233$), indicating that there may not be a genetic association in the RIF effect. Similarly there was a significant main effect between twin pairs for inhibition in the MZ control twins ($F_{(1:21)} = 60.559$, MSE = 9116.162, $p<.0005$, partial $\eta^2 = .752$. However the interaction was not significant for this group ($F_{(1:21)} = 1.864$, MSE = 280.584, $p= .187$, partial $\eta^2 = .085$).

<u>The RIF effect in MZ DC schizophrenia twins compared to their non psychotic twin member.</u>

Analysis of Variance revealed that the facilitation effect of practice was significant for MZ DC twins with schizophrenia $F_{(1:10)} = 1.154$, MSE = 4719.416 $p < .05$, partial $\eta^2 =$

.527 with participants demonstrating a greater recall of Rp+ items than Nrp items. The inhibition effect of practice was also significant for the MZ DC twins with schizophrenia, demonstrating greater recall of Nrp items than Rp- items $F(1:10) = 5.000$, MSE = 679.012 , $p<.05$, partial $\eta^2 = .333$

The analyses in the MZ DC non psychotic twins yielded an identical trend in results for both facilitation and inhibition. The facilitation effect of practice was significant with greater recall of Rp+ items than Nrp items, $F_{(1:10)} = 81.623$, MSE = 9664.703, $p < .0005$, partial $\eta^2 = .891$. The inhibition effects of practice was also significant, demonstrating a greater recall of Nrp items than Rp- items $F_{(1:10)} = 19.397$, MSE = 2840.909, $p < .005$, partial $\eta^2 = .660$

In order to determine if the forgetting effects were similar for the two groups, the data was combined into a mixed design ANOVA. This analysis yielded a significant main effect between the twin pairs in inhibition $F_{(1:20)} = 24.287$, MSE = 2831.650, $p < .0005$, partial $\eta^2 = .548$. However there was a significant interaction between patient / control and inhibition score $F_{(1:20)} = 7.393$. MSE = 861.953, $p < .05$, partial $\eta^2 = .270$with a greater Inhibition effect in the control twins than in the schizophrenia twins ($t = 2.03$, $p < .05$), indicating that although both the MZ DC twins and controls demonstrated a RIF effect; this RIF effect is less evident among the patients.

The RIF effect in DZ control twins

Analysis of Variance revealed that the facilitation effect of practice was significant for DZ control twins $F_{(1:43)} = 10.727$, MSE = 24109.158 $p < .0005$, partial $\eta^2 = .720$with participants demonstrating a greater recall of Rp+ items than Nrp items. The Inhibition effect of practice was also significant, demonstrating greater recall of Nrp items than Rp- items F(1:43) = 61.036, MSE = 10078.497 , $p<.0005$, partial $\eta^2 = .587$. Thus this group demonstrated the standard RIF effect. In order to determine if this RIF effect was significantly different within the twin pairs a mixed ANOVA analysis was conducted. This yielded a significant main effect of inhibition within each twin pair $F_{(1:43)} = 69.822$, MSE = 2831.650, $p < .0005$, partial $\eta^2 = .624$. However there was a significant interaction between the twin pairs and inhibition score $F_{(1:43)} = 7.190$. MSE = 1037.798, $p < .05$, partial $\eta^2 = .1.46$.

Neuropsychological tests and smoking in relation to the RIF effect in different twin groups

Table 4.3, shows the mean (± SD) scores of the different neuropsychological measures tested in the different twin groups. Bivariate correlation analyses were conducted for these measures and the RIF effect in order to determine whether the RIF effect was associated with any of these measures in each particular group.

Table 6.3. *The mean (± SD) scores of the different neuropsychological measures tested in the different twin groups.*

	MZ CC twins with Sz (n=22)	MZ DC twins with Sz (n=11)	MZ DC non psychotic twins (n=11)	MZ control twins (n=22)	DZ control twins (22)
BDI-II	10.45 (10.72)	9.63 (10.06)	10.66 (9.33)	8.13 (8.11)	9.29 (9.47)
HV- L	21.59 (3.91)	20.72 (4.24)	23.54 (1.14)	24.77 (4.18)	23.18 (4.31)
HV- D	8.68 (1.67)	8.36 (1.74	9.41 (1.72)	9.59 (1.56)	9.13 (1.66)
HV – R	9.68 (1.35)	9.54 (1.43)	10.08 (1.37)	10.31 (1.24)	10.00 (1.33)
Trail making A	50.39 (15.26)	42.19 (18.57)	35.27 (16.29)	28.97 (13.15)	28.25 (7.76
Trail making B	120.56 (43.83)	108 (8.59)	85.22 (36.96)	61.95 (21.35)	58.03 (20.97)
IQ	97.23 (14.50)	92.45 (12.49)	100.25 (9.78)	104.57 (15.48)	108.23 (14.49)
Cigarettes per day	22.56 (12.17)	25.14 (15.71)	12.63 (10.12)	10.98 (20.85)	11.52 (19.34)

Correlation analysis for MZ CC twins with schizophrenia and MZ control twins

Correlation analysis revealed (see table 5.4) that in the MZ CC twins there was a significant positive correlation for the RIF effect and the number of cigarettes smoked per day ($r = .332$, $p < .005$), the other variables remained non-significant including the BDI-II. In contrast among the healthy control MZ sample there was a very high negative significant correlation for the RIF effect and BDI-II scores ($r = -.746$, $p < .0005$). In addition the number of cigarettes smoked per day emerged as a significant positive correlation with the RIF effect in this sample ($r = .329$, $p < .05$).In the MZ control twin group no other variable significantly correlated with the RIF

effect. It is worth mentioning that in the patient twin sample IQ was close to significance (r = .404, p = .062).

Correlation analysis for MZ DC twins with schizophrenia and their non psychotic twin pairs.

For the MZ DC twins the learning element of the Hopkins Verbal Learning task positively correlated with the RIF effect(r =.570, p<.05). Also the number of cigarettes smoked per day significantly correlated with the RIF effect in this sample (r = .282, p<.005).In contrast the number of cigarettes smoked per day did not significantly correlate with the RIF effect in the MZ DZ non psychotic twin pairs (r=.159, p=.479).For this group, there was a positive significant correlation between the RIF effect and all three elements of the Hopkins Verbal Learning tasks; (the learning element) (r=.640, p<.005), (the delayed recall element) (r = .460, p<.05) and (the recognition element) (r = 446, p<.05).There was a similar pattern of association for Trail making B (r = .144, p = .062) and IQ scores (r = 414, p=.075) but neither reached the level of statistical significance (see table 5.4).

Correlation analysis for DZ control twins

Correlation analysis of the DZ control twins revealed that the number of cigarettes smoked per day (r = 335, p <.005) and the learning element of the Hopkins Verbal Learning task (r = 560, p<.005) was positively correlated with the RIF effect. The other variables remained non significant (See table 5.4).

Table 6.4. *Pearson correlations of neuropsychological measures, mood and smoking scores of the different twin groups.*

	MZ CC twins with Sz (n=22)		**MZ DC twins with Sz (n=11)**		**MZ DC non psychotic twins (n=11)**		**MZ control twins (n=22)**		**DZ control twins (22)**	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
BDI-II	.230	.302	-.009	.968	-.213	.341	-.746**	.0005	-.233	.297
HV- L	.030	.895	.570**	.006	.640**	.001	.307	.165	560**	.001
HV- D	.870	.700	.460	.031	.460*	.031	.446	.038	.307	.165
HV – R	.159	.470	.045	.844	.446*	.038	.045	.844	.072	.329
Trail making A	-.011	.960	.178	.427	.304	.168	-.041	.408	.042	.366
Trail making B	.030	.895	.421	.105	.144	.062	.024	.447	.027	.414
IQ	.404	.062	.341	.055	.414	.075	-.016	.308	-.123	.159
Cigarettes per day	.332**	.005	.282**	.005	.159	.479	-.329*	.029	.335**	.003

6.5 Discussion

The results of the present study revealed that there was a significant RIF effect in monozygotic concordant schizophrenia twins and monozygotic control twins. This indicates that the RIF effect is evident among the clinical population and controls thus providing evidence for a robust RIF effect. This is consistent with the previous research (Storm, Angello, and Bjork, 2011; Strom and Levy 2012).

This study also revealed that the RIF effect is significantly different between the MZ CC for schizophrenia twins and the MZ control twins, with patients demonstrating a significantly reduced RIF effect in comparison to the healthy controls. This finding is consistent with previous findings by Soriano, et al., (2009) who also reported a RIF

impairment in schizophrenia, using recognition cues. The results of this study are also consistent with other previous studies, which have reported RIF impairment in clinical samples i.e. ADHD, Depression and dementia of the Alzheimer type. However these findings contradict the findings of Nestor et al (2005) and AhnAllen, et al., (2007) who reported intact RIF among individuals with schizophrenia when compared to healthy controls.

The results from this study revealed that among a twin population the RIF effect is significantly different between the twin pairs for each different twin group indicating that the RIF effect may not be associated with heritability. Correlation analysis revealed that different neuropsychological measures vary in the association to the RIF effect among the different twin groups. However the number of cigarettes smoked per day positively correlated with the RIF effect in all groups except for the monozygotic discordant non schizophrenic twins. When considering mean and SD scores (12.63, 10.12) for this group it is possible that the number of smokers may not have been high enough to detect a difference considering the small sample of 11 participants. Also it was found that among the monozygotic concordant for schizophrenia group only the number of cigarettes smoked per day was positively correlated with the RIF effect while all other measures remained non-significant. Suggesting a strong association between the numbers of cigarettes smoked per day and the RIF effect consistent with the findings reported by Edginton and Rusted,

(2003) and also consistent with the view that cigarette smoking may selectively enhance cognitive function (Sacco, et al., 2005).

Studies on individuals with schizophrenia have also revealed positive effects of cigarette smoking or other forms of nicotine administration (patch, nasal spray) on neuropsychological test measures in schizophrenia patients. For example studies showed improved performance scores on cognitive tests in individuals with schizophrenia after cigarette or nicotine administration in pre–post or separate sessions crossover placebo-controlled designs, or better cognitive performance in individuals with schizophrenia maintained on cigarettes compared to those who had stopped smoking (Georgeet, al., 2002; Depatie, et al., 2002; Levin, et al., 1996). It is possible that failure in finding other correlations of RIF and the different cognitive measures used may have been hindered by nicotine effects, as the smoking rate was relatively high in the population of this study. Thus perhaps an improved performance was demonstrated on the measures used for this study. Evidence discussed has demonstrated that nicotine leads to improved cognitive performance including, attention and vigilance, spatial organization test, measurers of visual–spatial memory and verbal memory (Sacco, et al., 2005).

Among the monozygotic control group however the BDI-II emerged as a negative significant predictor of the RIF effect, despite the fact that the mean (SD) number of

cigarettes smoked per day was 10.98 (20.85). This finding provides further evidence to suggest that low mood or depression is associated with a reduced RIF effect, consistent with previous findings (Groome and Sterkaj, 2010; Harris, et al., 2010; Bauml and Kuhbandner2007). However the monozygotic control group is the only group that produced a significant association between BDI-II and the RIF effect. As discussed above there may have been confounding variables preventing a significant finding from emerging, for instance smoking before testing or generally the number of cigarettes smoked per day. It is also possible that the overall BDI-II scores for each group were not high enough for a significant association to emerge as the highest mean (sd) score was 10.66 (9.33). This is below the benchmark for depression although the standard deviation was rather high.

Moreover the present study further advances the current field by confirming that the RIF effect is a robust finding and significant impairment is evident among clinical samples using category cues. There are several possible explanations for the present contradictory findings in the literature. Firstly Nestor, et al., (2005) and AhnAllen, et al., (2007) used a different version of the RIF procedure to that used in the present study. Both of these studies used a cued recall procedure as their final retrieval test, whereas the present study used a category cued recall procedure. It has been established that free recall yields a stronger RIF effect than cued recall (Anderson, et al., 1994), but it also differs from free recall in that RIF scores include an element of output interference. Thus the discrepancy between the findings of the

present study, Soriano, et al's., (2009) and those of the two previous studies could possibly reflect the absence of output interference in the schizophrenia group, or it may simply reflect the greater statistical power made possible by the enhanced RIF effect achieved with the procedure used in the present study.

There are several limitations to this study; primarily in twin research the population sample is relatively small therefore there may be statistical power issues with these findings. Also simple statistical packages (i.e. SPSS used in this study) are not compatible for detecting genetic associations and more sophisticated packages are needed for instance genetic modelling. Therefore the findings of this study can only assume a non heritable association, but further and more detailed analysis will need to be conducted in order to address this issue more confidently.

Twin studies provide an important means of testing genetic aspects to improve the understanding of the level of heritability and environmental contribution on various aspects of cognition. However the sample used for this study is relatively small in the field of twin studies and therefore there may be issues with statistical power preventing a clearer result from emerging. Although no sufficient evidence was provided to support the hypothesis, an exploratory analysis was conducted where clinical and health twins were combined. Monozygotic and dizygotic twins were collapsed and the results the expected pattern indicating that RIF may be a heritable component, warranting further investigation. Thus future studies will need to focus on

a larger sample to fully establish an association with heritability and the RIF effect. Nevertheless the evidence provided from this study is consistent with previous literature on RIF and schizophrenia and with the series of studies within this thesis, confirming an impaired RIF in schizophrenia.

The findings did not provide evidence of a genetic association in relation to RIF inhibitory processes but do pave the way for further investigation. This is an important element to pursue as inhibition may be a factor that can indeed be a potential target for modification. This is an important novel contribution to research as thus far there have not been any studies that have investigated the RIF effect in a sample of twins. This finding provides a foundation for future research to establish ways in which modulating inhibitory processes underlying RIF can be modified particularly among the clinical groups. It is possible that therapeutic interventions may benefit from considering inhibitory deficits among clinical populations and investigate ways in which to enhance inhibition.

6.6 Conclusion

In conclusion this study has provided evidence for a robust RIF effect in a sample of schizophrenia and control twins. It emerged that the RIF effect is significantly different within twin pairs providing evidence that this aspect of cognition may not be associated with heritability. Findings also revealed that the RIF effect is significantly different between the patients and healthy controls, providing further support for inhibitory deficits in schizophrenia as outlined in chapter five. One sample of twins also demonstrated that the RIF effect was associated with low mood or depression providing further evidence that the RIF effect may be mediated. Finally in all groups but one the number of cigarettes smoked per day emerged as a positive correlate of the RIF effect. Consistent with the previous series of studies this study confirms a robust RIF effect that may be mediated by factors such as mood and cigarette smoking.

Chapter 7

RIF and Cognition in Healthy Controls

7.1 Introduction

This chapter will consolidate and analyse the healthy control data that has been acquired from the individual studies described in this thesis. The purpose of this is to establish whether in a non-clinical sample the retrieval induced forgetting effect is associated with the other areas of cognition that were also assessed. The increased statistical power that a larger sample size provides may bring to light any association of RIF and different cognitive measure that may have not been detected in the individual studies. In this section the focus will be on specific cognitive measures and their association with retrieval induced forgetting also taking into account the observed variations in mood and smoking behaviour. As the main aspects of RIF have been discussed in the previous chapters, this chapter will focus instead on those factors thought to mediate levels of retrieval induced forgetting.

7.1.1 Overview

As discussed in previous chapters, research to date suggests that the RIF effect is a robust finding and has been replicated with various modifications of the paradigm including tests of word stem completion (Anderson and others 1994, 2000; Anderson and McCulloch 1999; Bäuml and Aslan 2004), tests of recognition memory (Hicks and Starns 2004; Starns and Hicks 2004), implicit memory tests (Perfect and others 2002; Veling and van Knippenberg 2004), and tests using independent probes as retrieval cues (Anderson and Spellman 1995; Anderson 2003; Aslan, et al., 2006; Saunders and MacLeod 2006 and Bäuml, et al., 2005).

Moreover the retrieval-induced forgetting effect has proven relevant in a variety of settings such as eyewitness memory (Saunders & MacLeod, 2002; Shaw, Bjork, & Handal, 1995 false memories (Bäuml and Kuhbandner 2003; Starns and Hicks 2004), impression formation (Macrae and McLeod 1998), and stereotype representation (Dunn and Spellman 2003; Quinn and others 2004). Findings have also found an association between RIF and clinical disorders as outlined in chapters four and five. These experimental results suggest real-life implications of the mechanisms underlying the RIF effect, however factors associated with the mediation of the paradigm have been largely ignored. There is evidence demonstrating that the RIF effect is mediated by nicotine (Edginton and Rusted, 2003) and mood (Bäuml, Hung and Conway, M.A. 2004; Groome and Sterkaj,

2010and Bäuml & Kuhbandner, 2007). However studies in this field have concentrated on the underlying mechanisms associated with the occurrence of the RIF effect and very little research has looked at factors that may play a part in mediating the effect. It is therefore important to investigate mediating factors in order to increase the understanding of this paradigm.

7.2 Aims

The primary objective of the current study is to examine the retrieval induced forgetting effect in a larger group of healthy controls by grouping all of the healthy controls from the series of studies presented in the previous chapters to establish whether the RIF effect is associated with cognitive measures such as; mindfulness, rumination and depression as measured by the BDI. The study will also investigate whether the cholinergic system plays a role in modulating the inhibitory processes that underlie RIF. Based on the literature reviewed, and the findings reported in the earlier chapters there appears to be good evidence to suggest that the RIF effect is a robust finding observed when different test formats are used and across different populations. It is therefore hypothesised that:

i) There will be a significant RIF effect in this healthy population. There is also evidence that the RIF effect is associated with negative memories and with low mood, it is therefore hypothesised that:

ii) The BDI scores will negatively correlate with the RIF effect. It has been established that BDI and rumination are inversely correlated with mindfulness. It is therefore hypothesised that:

iii) Rumination will be negatively and mindfulness positively correlated with the RIF effect. Finally research has also shown that nicotine has positive effects on cognitive functioning and in particular it has been found to enhance the RIF effect. Thus it is hypothesised that:

iv) Smoking status and the number of cigarettes smoked per day will be positively correlated with the RIF effect.

7.3 Methods

Design

i) A Within-group analysis was conducted to establish an overall RIF effect among a healthy control population,

ii) A correlation analysis was conducted for each cognitive measure and smoking to examine associations between different cognitive measures and the RIF effect in a healthy control group.

iii) A stepwise liner regression analysis was conducted to establish whether the factors found to correlate with the RIF effect would emerge as significant predictors in a regression model.

Participants

In total this group comprised127 participants from Chapter 3 (study 1), 65 participants from Chapter 4 (study 2), 34 participants from Chapter 5 (study 3) and 55 participants from chapter 6 (study 4) resulting in a total number of 281 participants. The demographic characteristics of this combined control sample are outlined in Table 5.1.There was some variation in the number of participants completing the full battery of assessments. (In some of the individual studies for example, there were greater time constraints affecting the number of tasks that could be completed). The number of participants for each assessment measure is identified in brackets next to the respective measure.

Table 7.1: *Demographic characteristics of participants*

	Control (N = 281)
Smokers (%)	40%
Mean number of cigarettes smoked per day (± SD)	12.93 (15.20)
Age (mean years ± SD)	44.27 (± 11.28)
Years of Educ (mean ± SD)	12.63 (± 1.74)
Sex	
Male	111(49.1%)
Female	115 (50.9%)

Materials and Procedure

Materials used were those outlined in the general methodology section and respective chapters. The procedure for the administration of the RIF and other neuropsychological assessments and the completion of the BDI-ll, Rumination, SPQ-B and Mindfulness questionnaires followed the protocol employedinthe individual studies described in the previous chapters. The only difference in methodological procedure between the studies was that there was a variation in the number of tests conducted.

7.4 Results

The Retrieval Induced Forgetting Effect

Table 6.2.shows the mean percentages of correct recall and standard deviations in the final recall test. The percentage of correct recall in the retrieval practice phase was 94.61. A mixed ANOVA analysis revealed a significant effect of RIF for this entire healthy population combined ($F_{(1:302)} = 322.992$, MSE = 56421.460 $p < .0005$, partial $\eta^2 = .589$)confirming the occurrence of inhibition (difference between the percentage recall for Rp- and Nrp items) with participants demonstrating a greater recall of Nrp items than Rp- items. A further mixed ANOVA was conducted for facilitation (difference between the percentage recall for Rp+ and Nrp items) in the final recall test. The results of this analysis revealed a significant facilitation effect of

practice ($F_{(1:33)}$ = 654.799,MSE = 117002.690 $p < .0005$, partial η^2 = .744)with participants demonstrating a greater recall of Rp+ items than Nrp items.

Table 7.2 Mean % (±SD) of correctly recalled exemplars during the final phase (n = 303)

Retrieval Practice Status		
R+	Rp-	Nrp
83.84 (16.08)	29.82 (20.80)	48.78 (17.36)

Cognitive measures and smoking in relation RIF

Table 5.3, shows mean (± SD) scores obtained for the different cognitive tests and the number of cigarettes smoked per day. These means were correlated with the RIF effect to determine an association between these measures and the RIF effect, see table 5.4.

Table 7.3.*Mean(± SD) scores for BDI, Schizotypy, cognitive measures and the number of cigarettes smoked per day*

Measure	Mean *(± SD)*
BDI-II (n=281)	16.22 (11.45)
Schizotypy (n=226)	8.09 (5.14)
RRS (n=226)	21.72 (17.00)
Mindfulness (226)	54.53 (13.04)
IQ (n=174)	101.66 (5.30)
HV- L (n=174)	23.89 (4.42)
HV- D (n=174)	9.24 (1.62)
HV – R (n=174)	7.89 (2.85)
Cigarettes per day (n=281)	12.93 (15.20)

Table 5.4, shows Pearson's correlations between the RIF effect, BDI, Schizotypy, smoking and the different cognitive measures. The analysis revealed significant correlations between the RIF effect and the following measures; BDI (r=-393, p<.0005), RRS (r=-.163, p<.0005), HV-L (r=.234, p<.0005), HV-R (r=.217, p<.05). The number of cigarettes smoked per day was also positively correlated with the RIF effect (r=.268, p<.0005). The other measures were not significantly correlated with RIF (see table 5.4).

Table 7.4. *Correlations for the RIF effect and BDI, Schizotypy, smoking and the different cognitive measures.*

Measure	RIF
BDI-II (n=281)	-.393** (p=000)
Schizotypy (n=226)	-.027 (p.346)
RRS (n=226)	-.163** (p=.007)
Mindfulness (226)	-.049 (p=.231)
IQ (n=154)	.089 (p=.123)
HV- L (n=154)	.234** (p=.004)
HV- D (n=154)	.217 (p=.007)
HV – R (n=154)	.270 (p=001)
Cigarettes per day (n=281)	.268** (p=.000)

** = Significant (p < 0.01) *

Stepwise linear regression analyses

The scores for the cognitive measures that were shown to be correlated (p<0.1) with the RIF effect were entered as independent variables into a stepwise linear regression analyses, age, sex and years of education were entered as covariates. A significant model emerged ($F_{(1,225)}$ =17.319, p<0.0005) explaining 27% of the

variance (Adjusted R^2 = .068). The BDI-II(β = .457, p< .005), RRS (β = .340, p< .005) were negative significant predictors of RIF in this model with BDI-II being the strongest predictor. While the number of cigarettes smoked per day (β = .223, p< .05) emerged as significant positive predictors of the RIF effect.

Table 7.5: *The unstandardised and Standardised regression for the variables entered into the regression model explaining variance in RIF scores (n = 130).*

Variable	B	SE	β	p
BDI-II	-.457	.375	.203	.000***
RRS	-.340	.125	-.269	.001**
Cigarettes per day	. 223	.110	. 268	.017*

*= significant (p<0.05) ** = Significant (p < .01) ***= Significant (p < .001)

7.5 Discussion

The results from this study, demonstrate a significant RIF effect in this healthy population. This is consistent with RIF studies using a similar test protocol to that used here (Anderson and Bell, 2001; Gómez-Ariza, Lechuga, Pelegrina, and Bajo, 2005; Macrae and MacLeod, 1999)

The findings also confirmed that the BDI scores were negatively correlated with the RIF effect in that the higher the BDI scores the lower the RIF effect. This confirmed the second hypothesis, that BDI scores will negatively correlate with RIF i.e. lower mood is associated with weaker RIF. This is consistent with previous research that

has demonstrated a similar association between mood and the RIF effect (Groome and Sterkaj 2010; Bauml and Khusbander, 2007, Brennon 2012; Barnier, Hung, and Conway, M.A. 2004). The results of this study also showed that increased ruminative response scores were correlated with a weaker RIF effect. No such association was found in respect of mindfulness.

Thus the third hypothesis is only partially accepted, ‘‘iii) Rumination will be negatively and mindfulness positively correlated with the RIF effect’’. This is consistent with previous literature (Branstrom, et al., 2010; Frewen, et al., 2008; Raes, et al., 2009; Raes and Williams, 2010; Fritzsche, et al., 2010 and Gotlib, et al., 2004) in relation to rumination but not for mindfulness. It is possible that the mindfulness scores in this sample were not particularly high in that the mean (sd) was 54.53 (13.04) These are below the reported normative scores on the MAAS 55.5 (9.36) (Schmertz, Anderson and Robins, (2009).

The final hypothesis that ‘‘The number of cigarettes smoked per day will be positively correlated with the RIF effect’’ was accepted as the results showed this to be the case as a higher number of cigarettes smoked was associated with a stronger RIF effect. This finding is consistent with previous literature in the field (Edginton and Rusted, 2003).

The results from this chapter confirm and further strengthen the findings in the previous chapters, in that the RIF effect as measured by a category cued procedure is significant and that this effect is associated with mood, rumination and smoking. The important novel finding to emerge from the regression analysis in this chapter is the clear association between the RIF effect, BDI, RRS and smoking. (Smoking was identified as a predictor of RIF in the previous chapters). This analysis has therefore highlighted that the strength of the RIF effect is likely to be mediated by factors such as mood, rumination and the number of cigarettes smoked. These findings are in line with previous research. However, there are some potential limitations to be considered. When grouping the participants together the numbers were much greater for BDI than any of the other measures, which makes it more difficult to compare the relative impact of all of the different factors on RIF.

7.6 Conclusion

The results from this study have revealed that the RIF effect is significant and it is associated with mood, rumination and smoking. This provides evidence to suggest that mood, rumination and smoking status are variables that warrant further investigation in future RIF research. This therefore has implications for the theoretical accounts of RIF. This is the first study investigating the RIF effect in relation to different cognitive variables amongst a healthy population. Thus provides a novel contribution to research whilst further strengthening the findings thus far discussed in this thesis

Chapter 8

General Discussion and Conclusion

8.1 Introduction

This section will provide an overview of the main findings discussed in this thesis in relation to the main aims and hypothesis. A brief summary of each study will be outlined followed by an evaluation of main findings in relation to the current literature. Also limitations encountered in this thesis will be addressed followed by implications and a clear conclusion of the overall thesis.

8.2.1 Summary of Chapter 3 (study 1)

The purpose of this study was to investigate differences in category cued and recognition recall procedures of the retrieval induced forgetting paradigm. This was done in order to address controversies in the current literature and establish which procedure will produce the strongest RIF and therefore is better to employ for the remainder studies. One hundred and twenty seven healthy controls were tested with one procedure (counterbalanced) and three months later with the other. The findings from this study revealed evidence to suggest, regardless of the test procedure employed RIF is a robust finding, that is individuals who demonstrate a high RIF effect employing the category cued RIF testing procedure also demonstrate a high RIF effect when employing a recognition RIF testing procedure. It was also found that the strength of the RIF effect is more apparent using the category-cued

procedure thus justifying the employment of this procedure for the remainder of the studies. These findings provide an important contribution to research as to date no study has made use of such investigation, and has important implications for past and future research. Although the specific focus was not on reliability of RIF the findings could be interpreted to mean that RIF may be a reliable measure that is stable over time.

8.2.2 Summary of Chapter 4 (study 2)

The purpose of this study was to examine retrieval induced forgetting in a clinically depressed population in comparison to healthy controls. The focus of this chapter was on the cognitive functioning of this population and the impact of mood and smoking in relation to the RIF mechanisms. Sixty five individuals with depression and sixty five healthy controls were tested. The findings revealed that both patients and controls demonstrated a standard pattern of the RIF effect; this effect, however, was significantly lower among the patients in comparison to the healthy controls. The RIF effect was also found to inversely correlate with increased RRS scores and positively correlate with number of cigarettes smoked, providing evidence to suggest that these may be mediating factors of RIF. These findings provide an important contribution to research in terms of increasing the evidence for an association of depression and the RIF effect and providing support for previous findings from a larger and more powerful clinical sample.

8.2.3 Summary of Chapter 5 (study 3)

The purpose of this chapter was to examine retrieval induced forgetting in psychosis, with a particular focus on schizophrenia. A sample of thirty four schizophrenia patients and thirty four healthy controls were compared on a range of neuropsychological measures and the RIF task. The few current studies in this field are contradictory, with some reporting an impaired whilst others and intact RIF among this population. This study aimed to address these mixed findings by employing a larger sample size and monitoring potential mediating effects of factors such as smoking and mood. Data revealed that both patients and controls demonstrated a standard pattern of the RIF effect, similar to the pattern observed in individuals with depression (in chapter 4) although this effect was significantly lower among the patients in this study compared to the healthy controls.

The RIF effect was also found to inversely correlate with increased SPQ-B scores and positively correlate with number of cigarettes smoked, providing evidence to suggest that these may be mediating factors of RIF. These findings provide an important contribution to research in terms of increasing the evidence for an association of the RIF effect with schizophrenia from a larger and more powerful clinical sample. Thus indicating that inhibitory processes measured by the RIF paradigm are impaired in individuals with schizophrenia. This has important clinical and theoretical implications in terms of warranting further investigation into the

specific role of RIF in association with this disorder. Also indicating that treatment strategies targeting RIF mechanisms may prove a beneficial approach in clinical settings. Although further research is needed to underpin the underlying RIF mechanisms associated with schizophrenia

8.2.4 Summary of Chapter 6 (study 4)

The purpose of this study was to examine retrieval induced forgetting in a sample of twin pairs concordant and discordant for schizophrenia and a sample of healthy control monozygotic and dizygotic twin pairs. This study was designed to establish whether there is an association between RIF and heritability. Twin pairs with schizophrenia and healthy twins were investigated using the RIF paradigm and various cognitive measures. A measure of mood, schiziotypy and smoking status was recorded. A similar RIF effect was expected among the twin pairs to indicate a heritable aspect of RIF. However the findings did not provide sufficient evidence to support this hypothesis. Although it was discussed that there may have been statistical power issues as in an exploratory analysis where monozygotic and dizygotic twins were collapsed the expected pattern within twin pairs was found. To date this is the first study investigating RIF among twins; this in itself is an important contribution to research. This study also provides further evidence for an impaired RIF in individuals with schizophrenia and confirms an association of RIF with mood and smoking, consistent with previous chapters.

8.2.5 Summary of Chapter 7 (study 5)

The purpose of this chapter was to establish whether the retrieval induced forgetting effect is associated with any of the carefully selected cognitive measures in a larger healthy control group. This was achieved by summarising the results of all of the healthy control participants who participated in the series of studies in this thesis to increase statistical power. The results from this study revealed that the RIF effect is significant and is associated with mood, rumination and smoking. This provides evidence to suggest that mood, rumination and smoking status are variables to be considered as potential mediating factors in RIF research. Thus has implication for the theoretical accounts of RIF. This is the first study to take investigating the RIF effect in relation to different cognitive variables among a healthy populations, thus provides a novel contribution to research.

8.3 Evaluation of the main hypotheses

In light of the findings from study one, the first hypothesis that testing procedure will have an impact on the effect of Retrieval Induced Forgetting was rejected. The hypothesis was made based on speculative findings suggesting that recognition recall provides a superior measure of RIF. However there are no studies to date that have tested the difference between the category cued and recognition recall procedure by comparing the scores of one measure to the scores of the other following a time elapse. Thus although the hypothesis was rejected the findings hold

important implications for methodological accounts of RIF. These findings imply that RIF may be a stable measure over time and provide evidence in support of previous findings employing category cued testing procedures (Nolen-Hoeksema 2000, 2006; Conway, M.A. and Fthenaki, 2003; Groome and Grant, 2005, Groome and Sterkaj 2010).

The second hypothesis that the Retrieval Induced Forgetting effect will be impaired among the individuals with depression and the individuals with schizophrenia was accepted. This hypothesis was based on the tentative studies demonstrating a RIF impairment in depression (Groome and Sterkaj, 2010) and schizophrenia (Soriano, et al., 2009). Having addressed the issue of methodological procedures in the first study, this study further contributes to research by confirming that a RIF impairment is apparent among depression and psychosis. This implies that underlying mechanisms of RIF are associated with these disorders, indicating that targeting such mechanisms may be beneficial approach in designing therapeutic interventions for these disorders.

The third hypothesis ‘Retrieval Induced Forgetting may be a heritable trait was rejected. This study set out to examine whether twin pairs demonstrate similar effects in RIF. It also set out to investigate whether twins with psychosis differed in the RIF effect in comparison to healthy twins. Indeed the results demonstrated a

significant difference between the clinical and healthy twins, consistent with the findings of study two and three. Providing further evidence for and impaired RIF in clinical samples. Thus the second part of this hypothesis was accepted. The important contribution to research emerging from this study is the evidence that RIF may not be a heritable component but further research with larger samples is needed. Importantly this study was the first to investigate RIF in a sample of twins.

The final hypothesis that Retrieval Induced Forgetting will be mediated was accepted in light of the findings from all studies conducted for the purpose of this thesis and more specifically from the larger sample of grouped healthy controls. It was continuously demonstrated that low mood or depression is inversely associated with RIF scores. Whilst smoking status was positively associated with the RIF effect, providing evidence that nicotine enhances inhibitory underlying RIF consistent with the findings of Edginton and Rusted (2003) Based on the final study where all the data was combined it emerged that rumination was also inversely correlated with the RIF effect. This provides evidence to suggest that rumination is an important aspect to consider in RIF research in line with its association with depression and low mood.

8.4 Limitations

It must be acknowledged that this programme of research was subject to several limitations that may have implications for the interpretation of results, some more serious than others. A measure of IQ was calculated for the majority of the

participants, which provides a measure of overall intellectual functioning and an indication of learning difficulties. The BDI was also administered to each participant, providing a subjective measure of depression. Although participants were asked to report any history of mental illness and depression and IQ scores were obtained. A major factor that must be considered is the failure to objectively screen the healthy controls for any mental illnesses or learning difficulties. This is a serious limitation in that unreported confounding issues or those unknown to the participant may have interfered with the reported findings. It must be noted however that participants were asked to report any history of current mental illness the danger is that they may not have been aware of any pathology. Thus screening with SCID (structured interviews for DSM disorders) for example may have brought forth any issue enabling a firmer conclusion to emerge from the findings.

A further limitation is associated with the findings that smoking enhances the RIF effect but for the purpose of this data collection time of smoking was not controlled. That is participants were not instructed to refrain from smoking prior to testing, nor was information regarding the last cigarette smoked recorded. It is possible that participant smokers (patient and controls) may or may not have had a cigarette prior to testing potentially either favourably or adversely influencing their performance. For example participants who were smokers but who may not have smoked prior to testing may have been more anxious and less focused which could have been

detrimental to their overall performance. Likewise smokers who did in fact smoke prior to testing may have been more focused or motivated thus favourably influencing their results. However, for the purpose experiments smokers were not instructed either way prior to their testing session and most smokers tend to self-regulate nicotine levels particularly before effortful processing or concentration. However, future studies can design the research protocol to control for this factor.

In addition there is a design limitation related to the administration of the BDI test, as it was administered during the retention interval of the RIF task. This is arguably a flaw in the design due to the content of questionnaire, it is possible that this may have induced a low mood, thus interfering with the results as low mood is reported to be negatively associated with the RIF effect. However it must be noted this procedure was constant throughout and for each participant therefore any low mood induction was consistent for all participants, therefore eliminating any overall differential impact on the RIF effect. It could however be argued that particularly participants with depression are more susceptible to low mood therefore may have been affected more so than the controls. The decision was made to administer this test at this stage of the procedure to avoid unnecessary demands on the participants especially the clinical sample. It was considered that if the BDI was administered immediately at the start of the retention interval, they will move on to other unrelated activities, thus be distracted from the content of the previous questionnaire.

Participants were also made aware that the nature of some questions may perhaps be upsetting and were informed that they did not have to respond to any part which they were not happy with. Nevertheless it is still a methodological limitation especially considering that mood is associated with RIF.

Another limitation to consider was the testing environment, as some of the controls were tested in their own home, it may be argued that this created a more comfortable condition for them which may have led to a better performance. An alternative interpretation is that those tested at their own home may not have fully engaged with the study due to other distracters leading to a reduced performance. Although only a small number of participants were tested in their own homes very little impact is attributed to this factor in relation to the overall findings. Finally it is well documented that clinical populations have reduced motivation, thus this may have impacted upon the results, although the high performance on the Rp+ items suggests that motivation may not have been adversely affected.

8.5 Review of findings in relation to literature.

The findings summarised from this thesis are novel in many respects, as discussed above, the findings support and extend previous work with clinical (AhnAllen, Nestor, McCarley, and Shenton, 2007; Nestor, et al., 2005: Soriano, et al., 2009 Groome and

Sterkaj, 2010), and healthy control samples (Edginton and Rusted, 2003; Bäuml, Hung and Conway, M.A. 2004 and Bäuml and Kuhbandner, 2007). Despite the limitations that have been outlined in the previous section, these findings pave the way for future research in this field, and more specifically warrant detailed investigations of exact temporal boundaries associated with retrieval-induced forgetting(Garcia-Bajos, et al., 2009; Storm, Bjork, and Bjork, 2012; Chan, 2009; MacLeod and Macrae, 2001).

Improved understanding of neuronal functioning will also facilitate the knowledge of mediating inhibitory processes. This will shed light into the underlying mechanisms associated with the enhancement of RIF by the cholinergic system. As evidence discussed has reported that nicotine, a cholinergic agonist, increases inhibition of irrelevant items without affecting recall of relevant material in RIF (Edginton and Rusted (2003). It is possible therefore that modulation of the cholinergic system is a good target to focus on for improvement of inhibitory control in depression and individuals with schizophrenia. This may subsequently lead to identification of therapeutic targets for the treatment of depression and schizophrenia.

Ultimately the application of these findings to the wider world and specifically clinical settings is important. For this it is necessary to enhance the knowledge of inhibition related forgetting and retrieval. It has been well established that people tend to forget information that is related to memories they are actively trying to retrieve (Levy and

Anderson 2002; Anderson 2003), RIF research brings theory one step closer to understanding the mechanisms involved in this cognitive process. Understanding how this paradoxical memory phenomenon occurs and its association with other factors such as mood, smoking and clinical disorders including depression and schizophrenia appears promising as an approach to identifying and implementing the real life implications.

There has also been evidence suggesting that retrieval-induced forgetting occurs on tests of both episodic and semantic memory (Blaxton and Neely 1983; Bäuml 2002; Johnson and Anderson 2004). Findings have also demonstrated the RIF effect is retrieval specific; that is, it depends on the act of remembering itself. Repeated learning of parts of the material is insufficient to cause subsequent forgetting (Anderson, Bjork, and Bjork, 2000; Bäuml, 2002), but retrieval effort alone, regardless of its success, can cause retrieval-induced forgetting (Storm, Bjork, Bjork, and Nestojko, 2006). It is plausible to assume that factors such as mindfulness and rumination are closely linked to this process. Although the findings of this research only identified rumination as a predictive variable of the RIF effect, previous findings have suggested that mindfulness is closely related to successful memory.

Evidently mindfulness is influenced by factors such as psychosocial stress which has been reported to abolish retrieval-induced forgetting (Koessler, Engler, Reither and Kissler, 2009) and it is known that psycho-social stress is associated with depression

and schizophrenia. Therefore it is possible that identifying a means to facilitate the RIF effect possibly even in the earlier stages could prevent symptoms from developing into a clinical disorder. HPA-axis activity, as reflected in increased salivary cortisol, could mediate this release from retrieval inhibition (Koessler, Engler, Reither and Kissler, 2009). Although stress responses are often considered favourable evolutionary adaptations and may be associated with a reduction in the number of items available for recall, they are typically viewed as adaptive mechanisms (MacLeod & Saunders, 2008). However the problem arises when these mechanisms become maladaptive.

It has been well established that there are clearly a complex combination of factors contributing to depression and schizophrenia. The nature of the cause these disorders have been extensively researched and to date there is no clear explanation. The nature of this research simply focuses on one particular aspect which, based on the evidence from this research programme may associated with these disorders but makes no speculation as to causality. It is simply highlighted that RIF is impaired in these disorders when compared to healthy controls. For this reason it is argued that targeting the mechanisms with RIF may be a viable option for treating these conditions.

In general maladaptive inhibitory mechanisms will interfere with successful memory retrieval. In the general introduction it was discussed that the ability to forget certain

information that is irrelevant, redundant, out-of-date, damaging, or distressing is a vital function of human memory (Markowistch and Brand, 2010). According to early research this successful memory function depends on the interaction between an externally provided or internally generated cue and stored memory traces (Tulving 1983). When a cue is associated with several traces, selective retrieval of the desired memory is facilitated by inhibiting other memory traces associated with the same cue, thereby attenuating the interference caused by these competitors. However if this function is impaired in individuals with depression and schizophrenia it is not surprising that these conditions demonstrate an association with impaired RIF.

In the RIF paradigm efficient retrieval practice with category-plus-stem cues (e.g., fruits-or____) would entail inhibition of related category exemplars that fail to overlap with the provided stems, which ultimately makes these unpracticed exemplar traces less accessible in the ensuing recall phase. However, this process would appear to be impaired in individuals with depression and schizophrenia indicating a need for intervention. As this effect of RIF is predominantly attributed to inhibitory control mechanisms that are recruited to overcome interference caused by competing memory traces (Anderson and others 1994; Anderson and Spellman 1995; Anderson 2003) it is necessary to intervene at this level to facilitate this mechanism among these clinical populations.

Deficient inhibitory memory processes in depression and schizophrenia may be associated with triggering or maintenance of cognitive bias. In the example of Self Memory System (SMS) (Conway, M.A. 2005; Conway M.A. and Pleydell-Pearce, 2000) discussed in the general introduction individuals with impaired RIF may experience difficulties in correctly identifying a stable pattern of activation across all three levels of knowledge. Leading to a dysfunctional process of the "working self" due to the inability to facilitate or inhibit retrieval of certain memories depending on current goals. In the SMS, goals influence the encoding, storage, and retrieval of information to determine the content and accessibility of autobiographical memories (Conway, 2005). More research needs to be conducted in this field to determine the precise association of autobiographical memory dysfunction, RIF, depression and schizophrenia. It is very plausible that there is a close association considering that autobiographical memory has been found to recruit inhibitory mechanisms associated with RIF (Brainer, et al., 2004).

The findings reported in this thesis are also consistent with the inhibitory account of RIF, it has been argued that inhibition may not be a unitary construct but rather fractionated inhibitory processes (Miyake, et al., 2000). In combination with neuropsychological and neuroimaging research these findings suggest a high relevance of prefrontal regions in the selection and maintenance of relevant memory representations at the expense of currently irrelevant items (Johansson, Aslan, Bäuml, Gäbel and Mecklinger 2007). Therefore findings reported here are consistent

with this notion that perhaps individuals with depression and psychoses are not able to inhibit these irrelevant memories, providing further evidence for importance of the role of inhibitory processes in these conditions.

The study by Johansson, et al., (2007) examined the act of such processes as they operate. In these findings an involvement of the prefrontal regions in the selection and maintenance of relevant memory was identified. Research has reported that depression is associated with several brain regions and also with hyperactivation of the cholinergic system and decreased activity of the noradrenergic system. These aspects have all been related to RIF, and as such it is therefore possible that RIF may be a contributory factor in depression.

8.6 Summary and Conclusions

This thesis outlined a series of studies investigating the retrieval induced forgetting paradigm. It was consistently demonstrated that individuals with schizophrenia and depression have an impaired RIF mechanism in comparison to healthy controls. This was the main finding evidenced by this research, a crucial finding that holds clinical and theoretical implications for these disorders. In a clinical sense improving the understanding of inhibitory processes associated with RIF may enhance the understanding of potential causes, sustainability and treatment of such clinical disorders. This programme of research also addressed some important issues; firstly confirming the consistency and robustness of RIF whilst also addressing

methodological issues, secondly demonstrating that RIF is a measure which can be mediated by factors such as mood and smoking. These are all important factors that need to be taken into consideration when interpreting past and future RIF findings. Overall, it is concluded that inhibitory processes underlying RIF are integral aspects of cognition that are associated with depression and schizophrenia. Further research is needed to explore the nature and impact of these processes.

8.7 Recommendations for future research

It has become apparent that studies need to take into consideration a number of factors when examining the RIF effect, although some factors were explored here, stress was not one of them. Future studies need to consider stress levels and the association between the HPA axis and the RIF effect, in both depression and psychosis to enhance the understanding of this mechanism. Also further research needs to be conducted to establish specific inhibitory processes underlying RIF to enhance the understanding of this mechanism and its association with depression and psychosis. Studies establishing causality would also prove beneficial in terms of establishing suitable therapeutic interventions to counteract these disorders. It is well established that both depression and psychosis are conditions associated with many deficits including, cognitive, neuropsychological and physiological components. It is concluded that a more integrative approach is needed in order to extend the knowledge of the aetiology, sustainability and treatment of these disorder

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